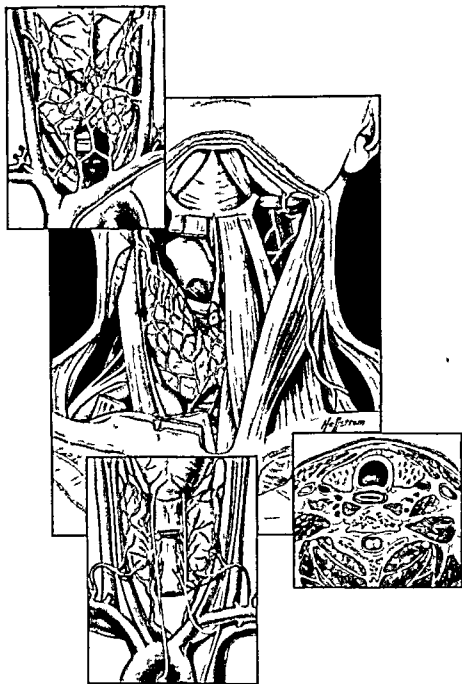


Pathology and Surgery
of
THYROID DISEASE



Anatomy of the thyroid gland and adjacent structures

Pathology and Surgery of THYROID DISEASE

by

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Dedicated
to
Cornelia Bickett DeCourcy

INTRODUCTION

IN PRESENTING this work, the authors acknowledge the principal sources, the thousands of cases, and years of experience at the DeCourcy Clinic. The work brings to date our more recent concepts of the thyroid gland and its pathology, as well as its surgical treatment. It is our aim to present this subject as a composite whole rather than as many unrelated facts.

The thyroid gland is a small organ with large potentialities. It is intimately connected with our bodily metabolism directly and, through metabolism, to the other endocrine factors of the body. Imbalance of one very often leads to imbalance of other glands.

We are concerned with both the hypo and hyper functions of the thyroid gland. To consider it either purely medically or purely surgically is not tenable. We must consider both aspects of therapeutics, especially in view of the more recent developments in this field, i.e., relationship of thiourea and thiouracil to the surgical approach.

We feel that in attempting to cover a subject of many ramifications, it is well not to assume that all readers have a common denominator of understanding and definition. We believe a brief review of anatomical and physiological principles to be in order and thus avoid later confusion. A consideration of this topic is also not complete without relating the historical background — the development of the subject over a period of time.

The section on surgical indications is followed by the surgical approach and the reader is given a complete view of its development through the years, particularly via the experiences and findings of the DeCourcy Clinic. These findings are the fruit of much mature thinking and experience. It is therefore hoped that our experiences will be of value and, if this be so, then the extensive labors expended in the creation of this work are justified.

PREFACE

THE great and in notable instances definitely revolutionary advances that have been made within the past few years in the fields of thyroid gland pathology and therapy would seem to justify the evolution of a new and comprehensive treatise not only incorporating the various phases of recent progress but also essaying a conservative and sound evaluation of them. The introduction of antithyroid drugs constitutes in itself one of the major developments in the long and complicated history of the treatment of hyperthyroid conditions. Indeed, some of the pioneer workers with the newer chemotherapeutic agents predicted that thyroidectomy for hyperthyroidism would become unnecessary in most cases. Of course, this early enthusiasm has been proved premature, and the thyrotoxic patient remains primarily a surgical problem. Nevertheless, the preoperative management of such patients has been modified and improved greatly and most gratifyingly, new methods have been generally adopted. Radio-iodine also has its place in the clinic — but not as a cure for any thyroid condition or even a satisfactory substitute for roentgen irradiation in the treatment of thyroid cancer. Radio-iodine would appear most useful in the location of aberrant thyroid tissue or metastases from cancerous glands. The setting forth of conservative conclusions — as justified by present evidence — along these lines should be widely helpful. Further, there is much that is new and enlightening to the clinician who encounters hypothyroidism in its varied manifestations, aberrant thyroid tissue, adenomatous glands, intrathoracic thyroids and above all, incipient or frank carcinoma of the thyroid. In short, thyroid pathology and surgery have of late undergone marked changes which — taken all together — signify practically a renaissance, of vital import to the clinician. Such considerations have been repeatedly brought to the attention of the authors by colleagues, including both physicians and surgeons, who have pointed out the need for a volume dealing with the newer knowledge of the thyroid gland with special reference to the requirements of the clinician and surgeon.

The first suggestion that such a book be written by us was made by

Donald J. Lyle, M.D., formerly of the DeCourcy Clinic and now Professor of Ophthalmology at the University of Cincinnati Medical School. His encouragement has meant much to us. It is also a genuine pleasure to acknowledge our deep gratitude to William McKee Germaine, M.D., Pathologist of the Good Samaritan Hospital, for his guidance and material assistance in the preparation of the chapter on Pathology.

Carroll DeCourcy, M.D., brother of the senior author, has been an inspiration not only in the writing of this book but also throughout our entire surgical career.

For their untiring efforts in our behalf we are indebted further to Robert Mansfield, M.D., whose knowledge and advice were most helpful in the work on Surgery, Embryology, and Anatomy, to Dr. Elbert Ruth, Associate Professor of Anatomy at the University of Cincinnati Medical School, who reviewed the sections on Embryology and Anatomy, to our associates of the DeCourcy Clinic Medical and Surgical Departments, who assisted in many ways, to Miss Wanda Giffin for her excellent secretarial work, in which she was assisted by Mrs. Julia Russell and Bernice Teaney, and to Mrs. John Hellstrom, whose drawings were exceptionally well executed, under the supervision of Mr. Joseph B. Homan, Associate Professor of Medical Art, University of Cincinnati Medical School. Finally, we express our appreciation to Mr. Charles C. Thomas and his associates for their counsel and manifold aid.

Cincinnati

The Authors

CONTENTS

DEDICATION	v
INTRODUCTION	vii
PREFACE	ix
I PREVIEW —SURGICAL ASPECTS OF THYROID DISEASE	3
Hypofunction	1
Hyperfunction	5
No Disturbance in Function	11
Summary	12
II HISTORICAL ASPECTS OF THE THYROID GLAND —PAST AND PRESENT—EUROPEAN AND AMERICAN	11
III EMBRYOLOGY	26
Clinical Significance of the Embryology of the Thyroid	26
Comparative Embryology	27
Embryology of the Thyroid in Lower Vertebrates	27
Embryology of the Thyroid in Man	30
Significance of the Ultimobranchial Bodies	32
Aberrant (Ectopic) Thyroid Tissue	35
Distinction Between True and False Aberrant Thyroids	36
Locations of Aberrant Thyroids	36
Other Developmental Anomalies	38
Absence of the Thyroid Gland	38
Absence of One Lobe	38
Absence of the Isthmus	38
Congenital Hypertrophy	38
Pyramidal Process (Lobe)	39
Anomalies in Relation to the Hyoid Bone	39
Thyroglossal Duct Anomalies	40
Thyroglossal Cysts and Istulæ	40
Intrathoracic Goiter	42
Lingual Thyroid	48
Lateral Aberrant Thyroids	51
Benign Metastasizing Colloid Goiter	55
Struma Ovarii—Ovarian Goiter	56
Fetal Adenoma	59
Time of Origin of Function of Thyroid	60

IV	ANATOMY HISTOLOGY, AND CYTOLOGY OF THE THYROID	66
	Gross Anatomy	66
	Weight at Birth	66
	Weight in Adults	67
	Relations with Cervical Fascia and Muscles	68
	Relation to the Parathyroids	69
	Blood Supply	69
	Divisions of the Superior Thyroid Artery	70
	Inferior Thyroid Arteries	71
	Thyroidea Ima	72
	Arterioles from the Trachea	72
	Periacinar Capillary Network	73
	Veins of the Thyroid Gland	73
	Lymphatics of the Thyroid	74
	Nerve Supply	75
	Histology and Cytology	76
	The Acini	77
	The Acinar Epithelium	78
	Effects of Thyrotropic Hormone	80
	Effects of Thiouracil and Related Substances	80
	Effects of Cold	81
	Intracellular Granules and Cell Inclusions	81
	Mitochondria	81
	Centrosome	81
	Fat Droplets	82
	Golgi Net	82
	Secretion Antecedents	82
	Intrafollicular Colloid	83
	Interfollicular Cells	85
	Interfollicular Epithelial Cells	85
	Nodules in an Otherwise Normal Gland	86
V	PHYSIOLOGICAL ASPECTS	92
	Physiology of the Thyroid Gland	92
	Secretory Activity	92
	Chemical Nature of Thyroid Hormone	92
	Calorigenic Action	94
	Actions on Growth and Development	95
	Relation of Thyroid Hormone to Food Factors	96
	Influence on Carbohydrate Metabolism	98
	Effects on the Nervous System	98
	Effects on the Circulatory System	99
	Hematopoiesis and the Thyroid	99
	Effect on Serum Cholesterol	99

Thyroid Hormone and Water Metabolism	100
Thyroid Hormone and the Metabolism of Inorganic Salts	100
Muscular Response to Thyroid Hormone	101
The Thyroid and the Endocrine System	101
Relation to the Pituitary	101
Relation to the Adrenal Cortex	102
Relation to the Adrenal Medulla	102
Relation to Sterility and Abortion	102
Relation to Menstrual Disturbances	103
Iodine and Thyroid Physiology	104
Substances Having Calorigenic Action	105
Hypofunction	106
Primary Hypothyroidism	106
Cretinism	106
Myxedema	107
Secondary Hypothyroidism	109
Simple Goiter	109
Nodular Nontoxic Goiter	109
Hyperfunction	110
Toxic Goiter	110
Symptoms and Signs	110
Response to Iodine	110
Hyperthyroidism in Pregnancy and Lactation	111
Regional Influences	111
Great Lakes Region	113
Mississippi Basin	115
 VI PHARMACOLOGY AND THERAPEUTIC ASPECTS	 121
A—IODINE METABOLISM AND BLOOD IODINE	121
Iodine Metabolism as Affected by Iodine Therapy	122
Significance of Blood Iodine Level	129
Iodine Metabolism in Relation to Liver Function and the Reticuloendothelial System	136
Iodine Medication in Thyrotoxicosis	142
B—THIOURACIL, PROPYLTHIOURACIL AND RELATED DRUGS IN TREATMENT OF THYROTOXICOSIS	149
Antithyroid Drugs	149
Thiourea	150
Thiouracil	150
Effects on Animals	150
Effects in Human Beings	151
Absorption, Distribution and Elimination	151

Thyroid Tissue after Thiouracil Therapy	152
Clinical Response to Thiouracil Therapy	153
Effect of Previous Iodide Therapy	154
Dosage	154
Synergistic Agents	155
Duration of Preoperative Medication	155
Toxic Effects	156
Theoretical Possibility of Carcinogenesis	158
Thiouracil in Hyperthyroidism Associated with Function ing Metastases of Adenocarcinoma	158
Thiouracil in Acute Thyroiditis	158
Thiobarbital	159
6 Isobutyl Thiouracil	160
Conclusions Suggested by Available Data	160
Propylthiouracil for Thyrotoxicosis	161

C—RADIOACTIVE ISOTOPES OF IODINE—USE IN THERAPY OF DIFFUSE TOXIC GOITER	166
Biochemical Investigations	169
Tracing Effects of Sulfonamides	169
Tracing Effects of Goitrogenic Substances	170
Metabolism of Radio Iodine as Affected by High and Low Temperatures	177
Iodine Metabolism in Graves Disease	177
Iodine Loss (Excretion)	179
Analysis of Thyroid Tissue After Operation	179
Radio Iodine in Childhood Hypothyroidism	180
Thyroid Carcinoma with Metastasis	182
Radioactive Iodine Therapy in Hyperthyroidism	186
Preliminary Studies	186
Dosage	188
Results Obtained with Radioactive Iodine (130 and 131) in Graves Disease	190
Side Effects and Possible Delayed Reactions	193
Element 85 Eka Iodine	194

VII PATHOLOGY	201
Diffuse Non toxic Goiter (Simple Colloid Goiter)	201
Diffuse Toxic Goiter	207
Formation of Nodules	206
Significance of the Staining Properties of Colloid	207
Adenomatous Goiter	207
Relation of Adenomas to Malignancy	210
Malignant Tumors	214

Histopathological Classification	214
Incidence	216
Incidence and Geographical Region	217
Age Incidence	217
Malignant Lesions of the Thyroid Gland in Childhood	218
Sex Incidence	218
Incidence of Different Histopathological Types	219
Malignant Adenomas	220
Papillary Adenocarcinoma	223
Other Types of Adenocarcinoma of the Thyroid	226
Adenocarcinoma Not Originating in Adenoma	226
Diffuse Adenocarcinoma	227
Small Round Cell Carcinoma	228
Scirrhus Carcinoma	229
Epidermoid Carcinoma	229
Carcinoma Sarcoma (Giant Cell Carcinoma)	229
Sarcoma	230
Operability Measures of Treatment and Prognosis	231
Discrete Adenomas	232
Operability	232
Operative Mortality	236
Results of Operation	236
VIII THYROIDITIS	241
Acute Suppurative Thyroiditis	243
Acute Nonsuppurative Thyroiditis	245
Riedel's Struma	247
Clinical Features	248
Differential Diagnosis	250
Pathologic Features	251
Gross Appearance	251
Histopathologic Features	251
Theories of Etiology	252
Role of Perithyroiditis	254
Hashimoto's Disease (Struma Lymphomatosa)	263
IX EXOPHTHALMIC GOITER	274
Role of Involuntary Nervous System	274
The Ocular Signs	276
Exophthalmos	276
Signs of Von Graefe Stellwag and Moebius	276
The Cause of Tachycardia	278
Why the Basal Metabolic Rate Is Increased	279
Origin of the Tremor	280

Vasomotor Symptoms	280
Gastro-Intestinal Symptoms	280
Symptoms Referable to the Thyroid Gland	281
X THE THYROID GLAND IN LATER LIFE	284
Changes in Later Life	286
Hypometabolism in Later Life	289
Hypothyroidism in the Elderly Patient	291
Hyperthyroidism in the Aged	291
Treatment of Thyrotoxicosis in the Elderly	294
XI PREOPERATIVE CONSIDERATIONS	300
Study of the Patient	301
Other Laboratory Tests	302
Importance of Experience and Judgment	302
Differential Diagnosis	303
Preoperative Treatment	304
Rest and Informal Psychotherapy	305
Diet	306
Treatment of Complicating Disorders	307
Cardiac Conditions	307
Diabetes Mellitus	307
Hepatic Insufficiency	307
Infections	307
Iodinization	308
Iodine in Conjunction with Thio Drug	312
Thio Drug Therapy	314
Thyroid Crisis	314
Prerequisites for Thyroidectomy	315
Prerequisites for Bilateral Thyroidectomy	315
General Physical and Mental Condition	315
Gain in Weight	315
Basal Metabolic Rate	316
Resting Pulse Rate	316
Complicating Disorders	316
Poor Risk Patients—Unilateral Thyroidectomy	316
Röntgenotherapy	317
Blood Pressure in Disturbances of the Thyroid Gland	318
In Exophthalmic Goiter	318
Relation of Blood Pressure to Basal Metabolic Rate	319
Hypertension and Glycosuria	320
Blood Pressure in Myxedema	321
The Problem of Goiter Heart	322

XII ANESTHESIA IN THYROID SURGERY	329
Intratracheal Anesthesia	331
Preliminary Sedation	332
Anesthesia in Operations Following Treatment with Thiouracil	333
Local Anesthesia	333
Ether	334
Ethylene and Ether	335
Cyclopropane	335
Intravenous Anesthesia	336
Tri bromomethanol in Amylene Hydrate	337
Spinal Anesthesia	337
Carotid Sinus Syndrome	338
Removal of Excess Mucus	338
XIII OPERATIVE CONSIDERATIONS	340
Technique of Bilateral Thyroidectomy	343
Amount of Gland to Remove	355
Possible Errors on the Operating Table	358
Unilateral Thyroidectomy	359
Removal of Discrete Adenomas	361
Removal of Malignant Adenomas	365
Removal of An Intrathoracic Goiter	368
Substernal Approach—Thoracic Approach	371
Thyroglossal Rests	372
Lateral Aberrant Thyroid Tissue	374
Ligation of Thyroid Arteries	375
XIV POSTOPERATIVE CARE	382
Care in the Immediate Postoperative Period	382
Sedation	383
Dangers of Oversedation	383
Iodine Therapy	384
Possible Postoperative Complications	384
Nausea and Vomiting	384
Hemorrhage	385
Infection	385
Hepatic Difficulties	386
Congestive Heart Failure	386
Auricular Fibrillation and Auricular Flutter	387
Collection of Mucus	387
Injury to the Recurrent Laryngeal Nerves	387
Other Causes of Laryngeal or Tracheal Obstruction	389
Thyroid Crisis	390
Treatment	395
Parathyroid Tetany	395

XV	POSTOPERATIVE SEQUELAE	400
	Postoperative Hypothyroidism	400
	Recurrent or Persistent Hyperthyroidism	401
	Causes	402
	Prevention	404
	Treatment	408
	Exophthalmos	409
	Increased Prominence of the Eyes Following Medical and	
	<i>Surgical Treatment</i>	409
	Marked Exophthalmos and Progressive Exophthalmos Fol-	
	lowing Thyroidectomy	411
	Causative Factors in Malignant Exophthalmos	413
	Disturbances of Ocular Muscles	413
	Importance of Periodic Examinations	414
	Rehabilitation	414
XVI	FUTURE OF THYROID SURGERY	418
	INDEX	425

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CHAPTTR I

PREVIEW

SURGICAL ASPECTS OF THYROID DISEASE

GLANCING over the years from the inception of our medical careers some thirty years ago the authors can well visualize the tremendous knowledge amassed concerning the thyroid gland, its diseases, and treatment. We, at the DeCourcy Clinic, have been fortunate in seeing more than the average number of such cases with a wide variety of syndromes.

The various dyscrasias of the thyroid have been recognized for many years but the relationship with the thyroid gland and the mechanism responsible have been little understood until fairly recently.

For instance, the story of goiter goes back to ancient times. For ages before iodine was known even before the Christian era, peoples in far spread sections of the world were using the ashes of seaweed and sponges, chewing the seaweed and even bathing in seaweed for the treatment of 'bigneck'.

In the sixteenth century Fabricus Aquapendente, an Italian anatomist and embryologist, described goiter as a disease of the thyroid gland. The relationship between iodine deficiency and goiter was established in 1852 by Chatin who compared the iodine content of soil and water in goitrous and non goitrous districts. It was not until the researches of Marine in the 1920's that any practical application of the subject was obtained. Marine succeeded in producing simple goiter in animals and man by reducing iodine intake and preventing it by the administration of iodine.

So far as we know, the thyroid is a gland of internal secretion whose sole function is the secretion and storage of its own hormone. This hormone, which was isolated in 1915 by Kendall, is the iodine-bearing amino acid, thyroxin. As the body's demand for the hormone varies and as the body does not provide any other storage, the thyroid gland itself must necessarily not only manufacture its hormone but must store the reserve. Thus, utterly dependent upon its hormonal activity,

the thyroid gland plays a vital rôle in the growth and metabolism of the individual

The structure of the gland is made up of numerous follicles lined by epithelium and surrounded by a rich network of capillaries and lymphatics. The active secretion is stored in the colloid, to be supplied by the body according to demand. The height of the cells is determined by the amount of colloid contained in the acini. When the acini have little or no colloid, the cells are columnar, when distended, the cells are cuboidal. The thyroid appears to be capable of functioning at birth and under normal circumstances reaches its maximum weight at the period of puberty.

Much confusion has arisen within the past years due to differences of terminology and classification of the various thyroid dyscrasias. Even more confusing are the actual misnomers, such as exophthalmic goiter which may be present in a patient with neither a demonstrable goiter nor exophthalmos. To my mind, a simple, concise yet comprehensive classification and uniform nomenclature are absolutely essential in order to approach an understanding of the subject.

A knowledge of the histopathological changes which occur in the diseased gland and correlation of the clinical and pathological findings are also essential for a clear conception of thyroid pathology.

Thyroid diseases may be divided on a physiological basis into three classifications, those in which there is (1) hypofunction, (2) hyperfunction, and (3) no apparent disturbance in function.

HYPOfUNCTION

The diseases due to hypofunction of the thyroid are *myxedema* and *cretinism*, in which the loss of functioning thyroid tissue is produced usually by primary atrophy of unknown cause, infection and occasionally by removal at operation. Scar tissue generally replaces the normal structure of the gland.

Secondary hypothyroidism sometimes occurs in patients with other endocrinopathies but in whom there is lack of adequate stimulation of the thyroid. Histologically, the gland appears in a resting state with flat or low cuboidal epithelium and colloid.

In these states, stimulation therapy with desiccated thyroid over a period of time will generally raise the basal metabolic rate to normal with abatement of symptoms.

HYPERFUNCTION

There are two distinct types of goiter in which there is hyperfunction of the thyroid gland. The clinical classification according to nomenclature suggested by the Committee on Classification of the American Association for the Study of Goiter is (1) *toxic diffuse goiter*, and (2) *toxic nodular goiter*.

The toxic diffuse goiter is the so-called exophthalmic or hyperplastic goiter. Every physician knows the symptoms—increased metabolic rate, tachycardia, with greatly increased pulse rate; loss of weight



Fig. 1 (x 160) Hyperplasia, diffuse type (Graves' disease)

with corresponding loss of physical strength, nervousness and emotional instability, tremor, thyroid enlargement, and flushing of the skin.

The toxic symptoms of the nodular goiter are very much the same except that *they are less marked in degree*. The extreme emotional instability peculiar to toxic diffuse goiter and exophthalmos are not present. *The principal difference* lies in that the patient with toxic diffuse goiter evidences goiter and thyrotoxic symptoms simultaneously,

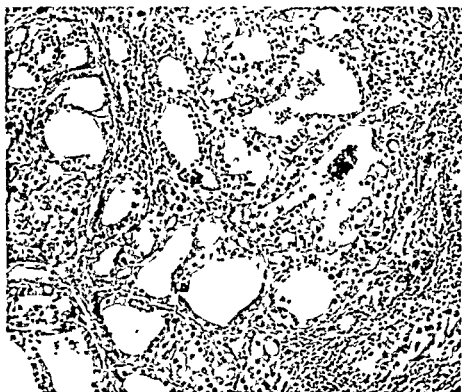


Fig 2 (x 160) Hyperplastic thyroid Graves type overtreated with iodides

whereas the patient with toxic nodular goiter will show thyrotoxic symptoms years after the onset of the goiter

The cause of toxic goiter is not known, although it is associated with overproduction of hormone. Most of the symptoms, however, may be explained on the basis of an imbalanced sympathetic nervous system subjected to the action of some circulating sympathomimetic toxin. Exophthalmos and the other ocular symptoms are due to stimulation of the sympathetic fibers by which the orbitalis and Mullerian muscles are innervated. Tachycardia results from stimulation of the cardioaccelerator centers in the cervical sympathetic ganglia. The increased basal metabolic rate seems to be due to two factors—namely, increased aeration in the lungs resulting from dilatation of the bronchial tubes and a direct effect from the hormone of the thyroid gland. The tremor is produced by irritation of the sympathetic nerve fibers distributed to all voluntary muscles.

Formerly we heard a great deal about the intermittency of the



Fig 3 (x 160) Nodular hyperplasia, with restorage and overstorage of colloid

symptoms of hyperthyroidism. The authors, however, have not been able to discern this unless, of course, the intermittency is brought about by a prolonged rest or medication.

Toxic diffuse goiter is quite commonly uniform in outline, whereas toxic nodular goiter is generally bosselated. Microscopically, toxic diffuse goiter shows proliferation or hyperplasia. There are papillary projections into the acini, decrease in the amount of colloid and in the iodine content and there is often increase in the lymphoid tissue between the follicles.

In toxic nodular goiter, there is usually no definite hyperplasia. The goiter is commonly of long standing and various degenerative changes may occur. These consist of thick bands of scar tissue, colloid degeneration, hemorrhage and formation of cartilage and bone.

In toxic nodular goiter, surgical enucleation of the affected portion of the gland is usually curative. Operation should be performed soon

after recognition of the condition to prevent damage to the heart. Operative mortality is very low and recurrence infrequent.

Subtotal thyroidectomy is indicated in toxic diffuse goiter with adequate preoperative and postoperative treatment. We do not believe that the thyroidectomy itself affects a cure but that it merely lessens the toxicity to a point where it becomes tolerable until nature can establish normal function. In other words, subtotal thyroidectomy provides a quantitative cure rather than a qualitative one. Toxic diffuse goiter has a tendency to cure itself and it is our opinion that it could do so if the host did not die first.

It is true that degenerative changes sometimes supervene in glands which have become quiescent. This usually occurs in later life and is manifested by myocardial changes without hyperthyroidism. The only apparent findings are fibrillation and palpable symmetrical enlargement of the thyroid gland. The basal metabolic rate may be normal or even subnormal and the patient more or less apathetic. Subtotal thyroidec-



Fig. 4 (x 160) Hyperplastic thyroid, Graves type, exhausted

tomy not only allows the heart to return to normal but increases the vitality of these patients

It is in the toxic diffuse goiter that administration of iodine produces such dramatic results. Lugol's solution ten drops three times daily will effect a reduction of the basal metabolic rate as much as three points daily, diminish tachycardia and allow the patient who has been losing weight to gain

In order to get the most benefit from iodine treatment, *it is important to know how it acts* in these cases. As the effect of iodine is transitory, it should not be given over long periods. Otherwise, the patient becomes iodine fast and the toxicity returns. When this occurs, even after time has elapsed during which no iodine is given, a second course of treatment seldom provides as favorable results.

An explanation of the transient action of iodine, it is our belief, lies in the changes occurring in the gland. In the toxic diffuse goiter, the thyroid gland is depleted of iodine and colloid. When iodine is administered, stasis is produced with distention of the acini with colloid which in turn exerts pressure against the surrounding vessels and secreting cells. Thus there is a mechanical block preventing the secretion from getting into the general circulation and suppressing the secretion of the cells. After a few weeks, however, the cells accommodate themselves to the increased pressure and secretion is again carried into the circulation with renewal of toxic manifestations. It is at this point that the patient is considered iodine fast.

Surgery for diffuse toxic goiter should never be attempted at this stage. Either the patient must be given a vacation from iodine and then reiodized at a later date or the operation must be performed in 2 or more stages. This is not so important in dealing with the toxic nodular goiter, as hypersecretion does not play such an important rôle.

It would be well for the thyroid surgeon to emphasize upon his mind these *two important factors in thyroid surgery*: (1) Toxicity may be present with normal or subnormal basal metabolic rate. (2) The proper use of iodine is imperative.

Adequate preparation must be instituted to bring the patient up to his optimum physically and mentally before surgery is employed. Thyroidectomy is never an emergency operation and should be carried out only when the condition of the patient justifies it. Postoperative crises usually mean inadequate preparation. The most important factors

to be considered are physical rest, mental rest, which includes freedom from anxiety and other emotional disturbances and strains, appropriate sedation, when required, diet containing 5 000 calories per day, and the proper administration of iodine

For well over a decade, all goiter patients at the DeCourcy Clinic have received ten minims of Lugol's solution 3 times daily for 2 to 4 weeks prior to operation as a matter of routine

The incidence of recurrent thyrotoxicosis following removal of toxic diffuse goiter has been reported as high as 25 per cent We have been able to maintain a recurrent rate of less than one per cent in several thousands of cases This we attribute to 2 specific procedures which we employ routinely First, there is adequate removal of the gland We have found by experience that it is necessary to remove at least four fifths of each lobe together with the isthmus and pyramidal lobe Secondly we have found that the administration of one half grain of desiccated thyroid extract twice a day for a period of at least a year will maintain the basal metabolic rate within normal limits and prevent recurrence

It would appear that the thyroid extract preserves the involution which was obtained prior to the operation with iodine If a permanent involution can be brought about in this way, we shall have gone a long way toward preventing recurrence

The postoperative administration of iodine seems to us to be a useless gesture As we have shown iodine does not alter the hyperplasia Since the portion of the gland remaining after thyroidectomy is still hyperplastic, iodine will not affect it

Although non toxic diffuse goiter and non toxic nodular goiter are generally classified as thyroid dyscrasias with no disturbance in function we are of the opinion that they are precursors to the toxic stage

Non toxic diffuse goiter is the adolescent or colloid goiter of early adult life It is characterized by a symmetrical enlargement of the thyroid with no clinical manifestations Histologically, it presents a normal appearing group of acini or alveoli greatly distended with colloid It has a tendency to respond to treatment with thyroid extract or iodine The authors have found desiccated thyroid extract one grain daily to be the preferred treatment Iodine treatment has frequently resulted in bosselations This has never occurred when thyroid extract was used

The fact that there is regression does not necessarily mean that there will be no recurrence. Microscopic examination of a large number of these thyroids has frequently revealed a beginning hyperplasia which has led us to believe that it may be a precursor of toxic diffuse goiter in many instances. Then too it has been demonstrated that histologically a non-toxic diffuse goiter presents the same reaction to iodine as toxic diffuse goiter.

It has been said that 1 out of 5 nodular goiters become toxic. It is questionable to the authors whether or not all nodular goiters are not toxic and the toxicity is not recognized. The goitrous condition generally exists for years apparently quiescent. It is not until discovery of fibrillation of myocardial damage that the toxicity is recognized. Enucleation of the nodules is generally advisable.

NO DISTURBANCE IN FUNCTION

The thyroid gland is also susceptible to the morbid changes to which tissues and organs in general fall heir, i.e. inflammation, congestion and neoplastic disease.

Thyroiditis although rare does occur in acute, subacute and chronic form and may be due to infection with any organism. It may be primary to the thyroid or follow infection of the teeth, throat or upper respiratory tract. The condition may subside spontaneously or it may become suppurative. Extensive involvement may cause some destruction of the gland with resulting hypothyroidism.

Although *Riedel's struma* is considered by many as a chronic form of thyroiditis, the authors feel that it is the result of a previous perithyroiditis which causes a partial constriction of the vessels entering the thyroid gland. As a result of the perithyroiditis the fibrous growth characteristic of the disease begins outside of the gland rather than within the thyroid proper. Histological evidence indicates that as a sequel to perithyroiditis and its complications there results a partial occlusion of the blood vessels entering the gland with subsequent formation of the fibrous tissue characteristic of Riedel's struma. Thus we believe that Riedel's struma is a vascular rather than a glandular condition. Treatment is subtotal thyroidectomy with removal of the mass.

Hashimoto's disease formerly etiologically associated with Riedel's struma by some authors is now quite generally recognized as a separate syndrome. Chronic lymphoid thyroiditis (Hashimoto) is charac-

terized by diffuse and extensive lymphatic infiltration, while in Riedel's disease the regional lymph nodes remain uninvolved. Though other symptoms are somewhat similar, in Hashimoto's disease the enlargement is bilateral in contrast to the usual involvement of one lobe in Riedel's. Hashimoto's disease usually occurs in women over forty, whereas the incidence is fairly equally divided between the sexes in Riedel's struma. In Hashimoto's disease, the thyroid is less fixed and much less adherent than in fibrous thyroiditis. Histologically, it shows numerous areas of lymphoid tissue with germinal centers and a few multinuclear giant cells. Surgery with subtotal thyroidectomy is indicated.

The only truly benign tumor of the thyroid is the *fetal adenoma*, which develops from a single nodule and is merely attached to the thyroid gland. Usually it does not become large enough to attract the attention of the patient before adult life. As the tumor grows older, it tends to undergo degeneration with production of toxicity. Its removal terminates the disease, unless operation has been deferred until constitutional damage has been caused. There is a tendency for these tumors to become malignant and for this reason alone they should be removed.

Most of the malignant tumors of the thyroid are epithelial in origin, arising in most instances from a preexisting adenoma, although they have been known to develop in toxic diffuse goiter. There is rapid metastasis, most frequently to the lymph nodes, mediastinum, lungs and bones. The metastatic lesions are often discovered before the presence of a primary growth is expected.

The possibility of primary cancer must be considered in every case of nodular goiter. It is unfortunate that no sign is pathognomonic and clinical recognition at an early stage is not always possible.

In all cases in which the tumor does not extend through the capsule of the gland or no distant metastasis can be perceived, total removal of the tumor mass is advisable, followed by x-ray treatment for the prevention of recurrence.

SUMMARY

An attempt has been made to give a *résumé* of the diseases of the thyroid gland *emphasizing the importance of uniform nomenclature and classification, the histology of the normal gland, the changes occur*

ring in diseases and the correlation of the clinical and pathological findings. These will be enlarged upon throughout the book.

The diseases have been classified on the basis of function. *Those of hypofunction*, namely myxedema, cretinism, and secondary hypothyroidism, are medical entities responding to substitution and stimulation therapy. *Those of hyperfunction*, namely toxic diffuse goiter and toxic nodular goiter, require surgery, that is, subtotal thyroidectomy. *Those of potential hyperfunction*, namely non-toxic diffuse goiter and non-toxic nodular goiter, respond to thyroid and iodine medication and to surgery, respectively. Among the dyscrasias in which there is no disturbance in function are the inflammations, acute, subacute and chronic thyroiditis (Hashimoto's disease), Riedel's struma, which is a vascular disease the result of a previous perithyroiditis, fetal adenoma and the malignant tumors. Thyroiditis, acute and subacute, is treated like other infections. Surgery is indicated in the other conditions. The newer medications, such as thiouracil and thiourea and also radioactive iodine, will be discussed in relation to the medical and surgical treatment of goiter.

CHAPTER II

HISTORICAL ASPECTS OF THE THYROID GLAND—PAST AND PRESENT— EUROPEAN AND AMERICAN

PROBABLY because of its high visibility when enlarged, the thyroid gland has been subjected for centuries to so much preliminary discussion and later investigation that a mountain of literature on the topic has arisen. Space permits us to present but a brief account of salient historical aspects. Reference will be made to classical papers of the past and also to most recent American and European contributions. Scientists believe that there is some merit in the method of forming a modern conception of a scientific subject by following the pathways blazed by the masters of the past.¹

Two millennia ago, Juvenal (60-140 A.D.) revealed in his XIIIth Satire that the thyroid was a structure familiar to the ancient Greeks and Romans when he wrote *Quis tumidum guttur miratur in Alpibus* — 'Who wonders at goiter in the Alps!' Pliny the Elder (23-79 A.D.) showed that the Swiss endemic disease was even then quite familiar. This premodern period in the development of our knowledge of the thyroid does not go far beyond simple recognition of the existence of the gland and a few empirical observations regarding it. The Romans did know that the gland swelled at critical periods in the sex life of women, and they made a practice of measuring the necks of brides as a test of prenuptial virginity. In this connection — since most of the information regarding the thyroid, up to and through the eighteenth century, deals mainly with descriptions of endemic goiter — it is interesting to note that the Madonnas of the old Dutch, German and Italian painters (fifteenth to sixteenth centuries) often reveal thyroid enlargement.

Claudius Galen (A.D. 138-201) had described the thyroid gland in his *De Voce*, and he had believed that it provided a lubricating fluid to the larynx and its cartilages to facilitate speech, — a theory that was

¹ James H. Means and Edward P. Richardson. *The Diagnosis and Treatment of Diseases of the Thyroid* (New York: Oxford University Press, 1929-1938), p. 3.

long accepted by eminent scientists (e.g., Malpighi) of the seventeenth century. In the course of epochs, others held theories that the thyroid was created to round out the neck in beautiful contours, to keep the throat warm, to protect the vocal chords, or to serve a mysterious purpose only during the prenatal stage of existence.²

No attention was paid to Galen's description until the Renaissance anatomist, Vesalius (1543), gave a fuller account. Tustachius (1552) applied the name *isthmus* to the part connecting the two lobes. Casserio (1601), also, like Vesalius, professor of anatomy at Padua, considered it a single organ in two parts, without an excretory duct. Wharton (1656) accurately delineated its location, size and weight, in addition to assigning to it the name *thyroid* meaning 'shield shaped' in Greek. He came quite near guessing that this gland secretes some substance to the circulating blood. De Bordeu (1776) set the stage for a theory of internal secretion with his doctrine that every gland, and even every organ of the body manufactures a specific secretion which enters the blood stream to produce a wholesome integration throughout the body.

Turning to the more important items from historical English American and French literature, we find that Prosser (1769) described a Derby neck, Moseley (1800) spoke of the Alpine bronchocele. The latter believed the cause to be human exposure to icy weather entering towns during warm seasons. The older literature favored the term *bronchocele* for goiter, although *trichecele* would have been more accurate. Barton (1800) ascribed to marshes the condition prevailing among the Oneida Indians of New York. In 1800 Fodéré termed goiter a relatively painless tumor of the thyroid, most frequently to be found in the inhabitants of Alpine valleys. He maintained that each little grain of the gland contained a juice which is greatly increased in engorgement, and that stagnation of this tumor leads to goiter — a notion not far from the truth as we know it.

It was the recognition of the effects of thyroid underfunction, as in endemic cretinism, rather than of overfunction, as in exophthalmic goiter, that enabled the true function and physiology of the thyroid to be first understood.

Although the Chinese employed the feeding of sheep's thyroids

² R. G. Henskins, *Endocrinology The Glands and Their Functions* (New York: W. W. Norton & Company, 1941) p. 65.

for cretinism as early as the sixth century A D (and the practice is observed today in China), substitution therapy advanced rapidly only after 1890. Meanwhile observations during each century were ripe. Roger of Palermo (1180) taught that the ashes of sponges and sea weed contain something that benefits goiter. In the sixteenth century, Paracelsus (1493-1541) noted the prevalence of goiter in the Duchy of Salzburg and, in agreement with modern writers, attributed it to the defective mineral content of the drinking water. He was shrewd to observe that endemic goiter coexisted in the same locality with cretinism or myxedema and that goiter is often associated with idiocy.^{*} Coindet (1820) had noted that dried sponge contained iodine and was successful in treating goiter. Chatin, from 1850 to 1860, carried out some of the first scientific investigations into the relationship between iodine and goiter; he showed that the iodine content of the soil, water and air of goitrous districts was very low, all attributing thyroid enlargement to this deficiency, recommended iodine administration as a preventive.

Simultaneously, research was going forward on cretinism. In 1848, Norris reported many cases of cretinism in a goitrous village of England and drew the opinion that the disease in question is not only accompanied but in some measure caused by the presence of goiter. The clinical picture of cretinism coinciding with endemic goiter was now becoming clearer in other regions apart from the Alpines. Curling (1850) revealed to the London Royal Society that he had found no trace of the thyroid gland at the autopsies of two sporadic cretins. Lagge (1871) made an excellent contribution to our knowledge of hypothyroidism by reporting four cases of sporadic cretinism which resembled endemic cretinism except for the constant absence of goiter. He reiterated that in the endemic form there is goiter, in the sporadic, absence of the thyroid body.

The first report of adult myxedema was written by Gull (1871), and this syndrome of adult cretinism or myxedema (mucoid swelling as it was named by Ord) is still often termed *Gull's disease*. Ord (1880) made the first of rare autopsies on the disease.

The problem of thyroid function continued to occupy so much thought that Horsley (1892) was able to gather ten theories regarding

^{*} Humphry Davy R. Ileson: *The Endocrine Organs in Health and Disease With An Historical Review* (London: Oxford University Press 1936) p. 158.

function, starting with those of Wharton. King (1836) made the keen observation that the high vascularity of the thyroid could not be designed solely for its own nourishment. His statements almost approach the modern concept that the gland secretes a thyroxin directly into the blood for the existence of the entire body. Cooper (1836) made the first extirpations of the thyroid in puppies in order to determine its function by observing the effects of its removal. But Schiff (1859) demonstrated for the first time that hypothyroid symptoms may follow in animals whose thyroids are extirpated. Zesas (1881) later confirmed Schiff. Schiff had undertaken his work at Geneva, and it was also in the goitrous regions of Switzerland that human thyroid surgery was developed. Both Reverdin (1882) and Kocher (1883) claimed credit for noticing postoperative hypothyroid symptoms. Kocher remarked that there was an obvious close relationship between a syndrome similar to myxoedema (*cachexia strumipriva*) and idiocy and cretinism.

In 1891, Schiff, using the antiseptics developed by Lister, again attacked the problem of thyroidectomy and found it was nonfatal in rats, but fatal in dogs and cats. He first successfully used substitution therapy by introducing into the abdominal cavity thyroid from another animal of the same species, a process which lessens the danger of thyroidectomy. In 1885, Horsley performed a complete thyroidectomy in monkeys to obtain a good imitation of human myxedema or *cachexia strumipriva*. This suggested that the human disorder was due to lack of thyroid.

Kocher's discoveries had stimulated research to such an extent that in 1883 the London Clinical Society appointed a committee (including Ord and Horsley) to investigate the entire topic of myxedema. In 1888, the committee based its monograph on 109 clinical cases and on Horsley's work. The series shows that the only common lesion is atrophy of the thyroid. Most of the committee's general conclusions have stood the test of time, namely, that myxedema is a well defined disease probably identical with sporadic cretinism and *cachexia strumipriva*, closely related to endemic cretinism and due to a loss of function of the thyroid organ. Gley (1891) revealed that when the parathyroids are also removed, then only do the nervous phenomena occur. This helped to clarify the distinction between thyroid and parathyroid glands.

Substitution therapy was coming to the front Bettencourt and Serrano (1890) relieved symptoms by grafting half a sheep's thyroid under each breast In 1891, Vassale prevented cachexia strumipriva in dogs after complete thyroidectomy by the intravenous injection of an extract of their own thyroids Murray (1891) first employed successfully a glycerine extract of sheep's thyroids for the relief of myxedema In 1892, two independent workers, Mackenzie and Fox, discovered that oral administration of thyroid constitutes an acceptable substitution therapy for myxedema

Concerning the nature of the thyroid's active ingredient, Baumann (1896) discovered that iodine in firm organic combination is a normal constituent of the gland tissue, subject to an increased concentration upon the further ingestion of iodine Marine (1907) demonstrated that iodine is essential for the normal function of the gland Hence, he regarded endemic goiter as a deficiency in iodine In 1915, Kendall accomplished the brilliant feat of isolating the crystalline form of iodine from the thyroid In 1917, he gave this hormone the name of *thyroxin* from selected letters of its chemical formula It is still disputed whether this material represents the true thyroid hormone

It was now obvious that the true and only function of the endocrine thyroid gland was to synthesize this iodine hormone and secrete it directly into the blood Today, normal and pathological physiology of the thyroid revolves around the action of thyroxin on the body and the factors which control its synthesis

To complete our historical survey, we must trace the threads in the development of knowledge concerning hyperthyroidism, or exophthalmic goiter It is strange that only simple goiters were known from antiquity to the nineteenth century, the striking syndrome of exophthalmic goiter being unrecognized

In 1802, the pioneer Flajani examined a young Spaniard with a tumor in the neck, which he recognized as thyroid Continuous dyspnoea, violent heart action, and swollen varicose like veins over this goiter were thus demonstrated to the world as some major manifestations of the exophthalmic goiter syndrome The period of discovery was now on Parry (1815, 1825) went on to give more complete and clearer descriptions of the syndrome based on several cases, omitting only the other important signs of tremor, sensation of warmth, and increased appetite Great as his powers of observation were,

nevertheless he deduced wrongly the thyroid's function. Graves (1835, 1838) emphasized the eye signs only in the fourth of his female cases. He believed the heart affection to be purely functional. More detailed items were reported from four cases by Von Basedow (1840), who is credited for the most complete description of the times. He made a differential diagnosis from other types of eye diseases, and stated that iodine was a helpful drug for goiter. Exophthalmic goiter, thus, is variously termed in different countries after Hajani, Parry, Graves, or Von Basedow, — who constitute the first period of discovery.

Almost all the symptoms with which we are familiar nowadays were recognized in a second period of discovery. Von Grafe (1864) described the so-called lid lag. Irlhne (1879) seems to have been the first to attempt an experimental causation of the disease in rabbits by cauterizing part of the corpora testiformia in the brain. Charcot (1885) practically confirmed Marie (1883) in his recognition that tremor is a constant sign in exophthalmic goiter. Marie also described urinary signs, diarrhea, sweating, morbid appetite, angina pectoris, tachycardia, and skin disorders. Moebius (1886) discovered the insufficiency of convergence known as his sign.

There entered a third period devoted to the development of the modern theories of the morbid physiology of exophthalmic goiter. Moebius (1891) developed the thyrotoxic theory. Although earlier French investigators had called it primarily a disorder of the nervous system, Moebius disagreed with this view, and held that Basedow's disease is related to an excessive function of the thyroid gland. Muller (1893) based his study of metabolic anomalies on clinical and post mortem examinations of cases, to discover an increased rate of protein metabolism, and an increased consumption of food combined with loss of weight. He concluded that exophthalmic goiter required for its production an hereditary neuropathic disposition plus a disorder of the thyroid. Magnus Levy (1895) confirmed Müller's view by showing that total catabolism is increased above normal not only in exophthalmic goiter but also in normal persons on the ingestion of thyroid extract, the converse being true in myxedema. Thus, Muller and Magnus Levy opened a wide field for further study of the understanding of the thyroid hormone in metabolism regulation.

Modern work on exophthalmic goiter advanced rapidly during 1900 to 1930. Cannon et al. (1914) experimented on cats to produce

a syndrome similar somewhat to exophthalmic goiter. The nerves he fused probably hooked up through the pituitary, for today similar results can be obtained by means of anterior lobe extracts. Plummer (1921) claimed that the physiologic function of the thyroid hormone is that of a catalytic agent accelerating oxidative processes in all tissue cells. Later studies by individuals have confirmed his claim of catalysis. In 1923, he proved that iodine has a characteristic effect in the disease to lower the metabolic rate and improve the symptoms. In this sense he greatly influenced modern management of toxic goiter. Aub et al (1927) showed that calcium and phosphorus metabolism in thyrotoxicosis are increased, while a decrease results in myxedema.

Bringing our survey of the thyroid gland up to the moment, we list a few major contributions that have resulted from the sea of research during the last two decades. Abelin (1932) has advised a diet rich in vitamins for it appears that vitamin A antagonizes thyroxin during an exophthalmic goiter. Wohl (1932-1936) has particularly directed attention toward cases that successfully masquerade as other entities with little to call attention to the underlying thyrotoxic substance. Zondek (1935) has reiterated in his monograph that endemic and sporadic cretinism are quite distinct, the latter being simply congenital myxoedema, the former being closely related to endemic goiter. Marine (1935) recapitulated the importance of the interrelations of the thyroid with other organs both of internal and of external secretion, but has added that as to our knowledge in this field only a good beginning has been made. He feels that thyroxin appears to be the active part of the thyroglobulin molecule secreted. Bartels and Perkin (1937) have shown that liver function is disturbed more often than has been commonly believed, and finally, the Study Committee on Endemic Goiter of the American Public Health Association has reported at its initial meeting that today iodine prophylaxis against goiter is most widely recognized, while iodized salt is used throughout the entire United States, and even in the Philippines, — a most beneficial outcome of Marine's investigations.*

At the present date, the discovery, experimental development and clinical application to hyperthyroidism of the drug *thiouuracil* is bring-

* Council on Foods and Nutrition: *Handbook of Nutrition: a Symposium* (Chicago: American Medical Association, 1943), p. 112.

ing great hope that at last the disease may be controlled by medical treatment. Newman, reviewing the literature up to 1945 in order to assess the future rank of the drug in therapy, finds that there is some dissatisfaction with previous methods of treatment by iodine therapy or thyroidectomy. Before the discovery of the new drug, substances which produce goiters amenable to iodine administration were already known, but a new group of substances whose action was *not* abolished by iodine administration began to come under observation. While testing the antibacterial effects of sulfonamides on rats, the Mackenzies (1911) found incidentally that there was great enlargement of the thyroid glands. Their subsequent investigation, in 1913, showed that sulfonamides and thiourea compounds all produced lowering of the basal metabolic rate and enlargement of the gland with loss of colloid. The effects on the thyroid gland were abolished by thyroxin administration, but *not* by giving iodine. Astwood (1913) finally selected thiouracil for clinical use in the treatment of hyperthyroidism. Theorists postulated that thiouracil interferes with the manufacture of thyroid hormone by the gland, thus diminution of secretion then eliciting an increased output of pituitary thyrotropic hormone which stimulates an enlargement of the thyroid gland. It was found that a thiouracil treated gland shows marked inability to utilize injections of radioactive iodine, in hyperthyroidism the level of protein bound iodine, with which basal heat production is correlated, is elevated, but after treatment with thiouracil the level falls. Numerous experiments are still in progress to determine more clinical and physiological reactions of thiouracil — for inhibition of function in an endocrine gland by the administration of chemical compounds is a new field of investigation in the history of endocrinology.

A final glance at other problems concerning the thyroid reveals that recent research fairly bristles with thought provoking questions. Is thyroid disease an element responsible for behavior problems in children? Shall psychotherapy be made a major factor in the treatment of exophthalmic goiter? What part has the thyroid played in evolution and in the intellectual progress of various races? What function does the thyroid gland have in the slowing down of age? Will more refinements in operative technique completely abolish the present low mortality rate? Is there any significant relationship between the hor

none and a vitamin control? Do the immunity processes of the body depend somewhat upon the thyroxin secretion?

The secret of the thyroid gland would seem to lie in a further understanding of its biological, pathological, and surgical aspects

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CHAPTER III

EMBRYOLOGY

CLINICAL SIGNIFICANCE OF THE EMBRYOLOGY OF THE THYROID

THE EMBRYOLOGY of the thyroid gland provides a basis for the logical classification and clear understanding of many pathological conditions encountered in the clinic. Thus, embryological studies extending through more than fifty years have important bearing on the problem of the potentially malignant nature of aberrant thyroids in general and lateral aberrant thyroids in particular, as recent investigations emphasize.

Developmental anomalies of the thyroid in relation to the hyoid bone and to the persistence of various portions of the thyroglossal tract are of the utmost importance to the surgeon, and precise knowledge of the possibilities invariably facilitates optimal treatment and indicates just what cases should be followed with the greatest care postoperatively in view of the probabilities of recurrence of thyroid tissue lesions.

If any one concept from this vast field may be described as outstandingly significant among innumerable vital considerations, we believe that it must be the realization of the capacity of thyroid tissue to establish and maintain independent growth outside the definitive thyroid gland. Certainly no other tissue presents more or greater problems of growth extension, occurrence of ectopic masses and embryonic rests, and development of malignancy by structures apparently indistinguishable, in many instances, from so called benign growths in normal or abnormal locations. Furthermore, the capacity of aberrant thyroids to become functional, increases conspicuously the scope of the clinical considerations involved and gives them certain unique aspects.

COMPARATIVE EMBRYOLOGY

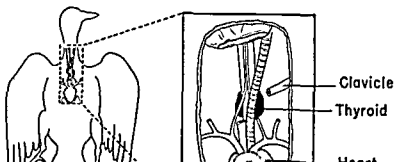
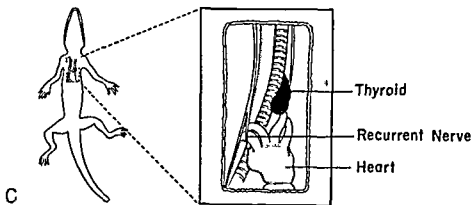
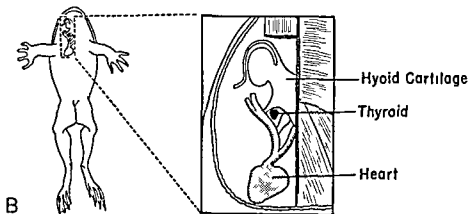
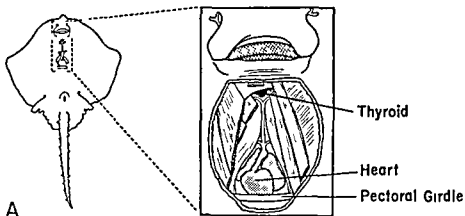
In terms of comparative embryology, the thyroid gland is an unpaired derivative of the primitive pharyngeal floor. The gland is a direct descendant of the endostyle organ which is present as a ventral midline outpocketing of the pharyngeal region in the most primitive chordates—the tunicates, amphioxus and ammocoetes. The endostyle organ is not found in chordates higher than the cyclostomes because of the evolutionary changes that have transformed it from a gland of external secretion into a gland of internal secretion. The endostyle or ancestral form of the gland in the lowest chordates is an important digestive gland, a dependency of the esophagus. Nevertheless, evolutionary change to endocrine function still leaves the altered glandular tissue—the evolved thyroid—with profound influences over digestive processes and nutrition in general. Thus, evolutionary embryology emphasizes the anciently established participation of the gland in physiology at profound or basic levels, thyroid hormone having vital effects on human basal metabolism and probably all other phases of nutrition.

EMBRYOLOGY OF THE THYROID IN LOWER VERTEBRATES

In the lower vertebrates—fishes, amphibians and reptiles—the thyroid gland definitely originates from a single median ventral invagination of the pharyngeal entoderm in the region just in front of the first branchial cleft. Remak stated that in birds also the gland arises similarly, from an unpaired median invagination of the pharyngeal epithelium in the neighborhood of the first branchial cleft. Remak further noted that later the anlage divides into a T-shaped mass which migrates with the aortic arches to its final intrathoracic position, the thyroglossal tract and isthmus being absorbed.

A generation later, however, Stieda (1881) asserted that the avian gland has a lateral as well as a median origin. In studies on the chick, Mall supported the belief of Remak and concluded that the derivatives (Korpen Y) of the fourth branchial cleft do not contribute to the development of the thyroid. According to Marine, subsequent work has confirmed the view of Remak (and also W. Müller as well as Mall) that, in birds, the thyroid is derived solely from the single median pharyngeal anlage in the region of the first branchial cleft.

These studies in comparative embryology have had important bear



←
Fig 5 *Comparative Anatomy of the Thyroid Gland* The thyroid gland of vertebrate animals arises either as a diverticulum, or as a solid cord of cells from the buccal floor at about the level of the hyoid arch. A cavity forms secondarily, by cytolysis, in those forms in which the thyroid anlage develops as a solid cord

During later development the thyroid undergoes characteristic changes in form and position in the different subdivisions of the vertebrata. In all of the high vertebrates this organ becomes constricted off from the pharynx in the course of development, and the communications between them are obliterated as they assume the definitive position characteristic of a particular subdivision of the vertebrate group. These characteristic positions are of interest inasmuch as they may suggest a phylogenetic explanation of the various positions in which aberrant thyroid tissue is found in man — with the exception of that thyroid tissue occasionally found in teratomas.

The primitive vertebrate, amphioxus, develops a groove or trough in the floor of the pharynx. This groove extending from the mouth to the stomach, is known as the *endostyle* and secretes a sticky mucus that entangles food particles. A similar structure morphologically the same, develops in the pharyngeal floor of *Ammocoetes* (the larval form of the Cyclostome, the lamprey *Petromyzon*). It is now generally accepted that this gives us the clue to the phylogenetic history of the thyroid gland. The slit like pharyngeal opening of *Ammocoetes* is gradually reduced until it becomes a small pore. During metamorphosis the pore is obliterated and the organ becomes a small vesicle underlying the pharynx. This vesicle gradually becomes divided into a number of small vesicles, and its secretion accumulates as a colloid substance like that of the thyroid vesicles of the higher vertebrates.

In the Elasmobranch fish, the skate, the thyroid tissue appears as a diffuse brownish mass located in front of the anterior fork of the ventral aorta, just posterior to the mandibular arch. The frog, a tailless amphibian, has a pair of thyroid glands located in the floor of the mouth, one gland between the posterior lateral process of the hyoid cartilage and the thyrohyoid process on each side. Among the reptiles the turtle has a single thyroid gland lying immediately anterior to the heart in the angle of the fork of the brachiocephalic artery, and the alligator has a single transversely elongated thyroid located on the ventral wall of the trachea, a short distance in front of the heart. The thyroids of both of these forms lie in the pleuro-peritoneal cavity. The birds on the other hand, have paired thyroids, located at the root of the neck, in the thoracic (pleuro-peritoneal) inlet. The thyroid glands of the pigeon are located along the common carotid arteries at the level of their origin — between the carotid and the trachea on the left side, and between the carotid and the gullet on the right side.

ing on the much debated problem as to the possible contribution of derivatives (ultimobranchial bodies) of the fourth branchial cleft to the development of the thyroid parenchyma in man. This problem which has pathological and clinical aspects, we shall discuss in a later section.

EMBRYOLOGY OF THE THYROID IN MAN

In early somite human embryos, the rudiment of the thyroid gland first appears as a thickening of the endoderm of the floor of the pharynx between the ventral extremities of the first and second pairs of gill pouches. The pharyngeal pouches, of course, develop as growth expansions of the branchiogenic pharynx differentiated in a cephalocaudal sequence and separated by the growth of the mesoderm (the arches). By the evagination of the thickening endoderm from which the thyroid originates, a median diverticulum is formed just caudal to that portion of the floor of the mouth which gives rise to the tuberculum impar.

At the 5 mm stage, the outgrowth is a minute flask shaped structure attached to the buccal cavity by a narrow, median stalk — which becomes the thyroglossal duct (strand, tract). It is located in front of the second arch mesoderm and is in direct contact with the endothelium of the aortic sac. The duct elongates and develops into a solid cord, which bifurcates at its lower end so that the terminal glandular swelling gives rise to two buds — the future thyroid lobes. Ordinarily, the bifurcation is in front of the developing larynx and forms the isthmus.

In man, a definite, patent duct may or may not be present during the embryological development. If a canal is present, its opening is the foramen cecum at the base of the tongue, the duct is usually obliterated by about the eighth fetal week. A duct that remains patent (as in some animals, e.g., amphioxus) or is not completely obliterated may give rise to cysts of the neck, fistulas and aberrant thyroids.

The thyroglossal duct is lined with a single layer of cylindrical epithelium, frequently ciliated. Exceptionally, a layer of pavement epithelium forms the duct lining. The same cylindrical structure is at first found in the terminal portion of the thyroglossal duct, which portion later develops into thyroid gland tissue. Even at about the fifth

or sixth fetal month, the thyroid gland is constituted of alveoli lined with a single (or double) layer of ciliated epithelium

At about the end of the fifth fetal week, the hyoid bone is represented by a cartilagenous mass behind the thyroglossal duct. Development of the hyoid causes a forward bending of the duct, which becomes intimately connected with the periosteum of the hyoid—thus, the frequent attachment of the pyramidal process to the hyoid is explained. Because of the growth of the hyoid bone, at about the ten mm stage (or toward the middle of the second month of intrauterine life) the thyroglossal duct ruptures, usually near its midpoint. The superior portion (lingual portion) extends from the foramen cecum of the tongue to the hyoid bone. The inferior, or thyroid, portion extends from the hyoid bone to the isthmus of the thyroid gland. Occasionally, rupture of the duct does not result from growth of the hyoid and in such cases the duct may develop as a continuous canal running from the foramen cecum to the isthmus of the thyroid gland.

Normally, beginning at about the fifth fetal week, the thyroglossal duct undergoes gradually atrophy and absorption following the formation of the developing thyroid lobes and the isthmus. As a result of this atrophy, generally only a fibrous cord, the thyroglossus tractus of His, remains, the cord extends from the foramen cecum of the tongue to the isthmus of the thyroid. In some cases, the thyroglossal tract may extend beyond the thyroid and into the anterior mediastinal space, at times to reach as far as the aorta. Obliteration of the thyroglossal duct is usually complete at about the eighth fetal week.

At the time of rupture of the thyroglossal duct (middle of second month of embryonic life), the growing thyroid is represented by a solid mass of cells draped across the upper part of the developing trachea. Soon thereafter, this median primordium of the thyroid fuses on each side with a ventral component (ultimobranchial body) of the fourth pharyngeal pouch. Within the solid mass of cells, branching plates of epithelium, one or two cells in thickness, take rise, so as to form closed cavities, which are the precursors of the follicle lumina. The cavities increase in size, some intercommunications at times developing, and eventually open to the outside, so that invasion by the vascular mesenchyme ensues.

As the ingrowth of connective tissue and blood vessels continues,

the epithelial plates break up into isolated cords, or solid epithelial bands. The cords or bands undergo lumina formation as their cells become rearranged and proliferate, primary follicles thus taking rise. At about the fifty mm stage, secondary follicles develop either by a process of budding off or by constriction of portions of the primary or parent follicles. Colloid is not formed until the sixty mm stage, the gland becoming functional probably soon thereafter.

SIGNIFICANCE OF THE ULTIMOBRANCHIAL BODIES

Studying sheep embryos, Stieda came to the conclusion that the entire thyroid gland is derived from the two paired bodies of the fourth branchial cleft—the lateral thyroid anlagen, as he termed them.

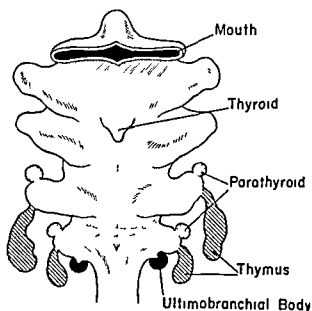


Fig 6 Ultimobranchial bodies

Investigating the embryo of the pig, Born confirmed the existence of the lateral thyroid anlagen but demonstrated that thyroid tissue is definitely formed from the median anlage, which fuses with the lateral thyroid anlagen. Working with human embryos, His concluded that the lateral lobes of the thyroid are derived from the lateral anlagen whereas the isthmus and pyramidal processes arise from the median anlage.

Later, Kastschenko denied, on the basis of his work with sheep

embryos, that the "lateral thyroid anlagen" give rise to any part of the thyroid. Van Bemmelen made comparative studies and concluded that the following structures are homologous: (1) the 'suprapericardial bodies' of elasmobranchs, (2) the 'postbranchial bodies' (Mauer) of amphibians, (3) the "Korpen Y" (Mall) of chicks, and (4) the "lateral thyroid anlagen" of mammals. Subsequent embryological investigations have established the fact that in all vertebrate classes except the cyclostomes, caudal to the last definite pouch (in man the fourth branchial cleft) a further evagination appears but does not attain morphologic value as a branchial pouch because it does not make contact with the mesoderm. (Nevertheless, some authors apply the term "fifth branchial pouch" to this formation.) This further evagination is a derivative of the ventral and larger part of the fourth branchial pouch, its embryological fate is debated even today, being highly significant in relation not only to the origin of thyroid parenchyma but also to the development and pathology of so-called "lateral aberrant thyroids." (Recent investigations have all but proved the great clinical importance of considering 'lateral aberrant thyroids' as potentially malignant metastases from a primary focus in the homolateral lobe of the thyroid proper.)

Mauer (1899) and Herrmann and Verdun supported the view of Kastachenko that "lateral thyroid anlagen" do not participate in the development of the thyroid. These workers stated further that in monotremes and marsupials these structures and bodies derived from them remain for the most part separate from the thyroid, but that they generally do become imbedded in the posterior lateral portions of the thyroid lobes. Grosser suggested that, subsequent to their fusion with the median anlage, the so-called "lateral thyroid anlagen" degenerate, for those "postbranchial bodies" he proposed the term "ultimobranchial bodies" because it appears that in the human embryo they take rise from the rudimentary fifth branchial cleft rather than the fourth.

Kingsbury (1914) tentatively confirmed Grosser's suggestion but stated that the human material available was inadequate for such a cytologic conclusion. Badertscher (1918), studying pig embryos and fetuses, found mitoses and not degenerating cells in the cell cords and masses derived from the ultimobranchial bodies. Rogers (1927), after extensive researches on the histogenesis of the thyroid of the rat reported similar findings. He concluded that, because colloid containing

follicles appeared to develop in all the cords in the region where the lateral thyroid (ultimobranchial body) was located, these bodies must form at least some thyroid parenchyma which cannot be distinguished histologically from any other portion of the gland. Rogers believed that, in all probability, the contribution of the ultimobranchial bodies to the thyroid parenchyma must be small.

Watzka's 1933 report supported the conception of the ultimobranchial bodies as potential precursors of glandular tissue of internal secretion; he stated that their structure, composition, size, nerve and blood supply necessitate this concept of their significance. Nevertheless, he did not agree that these bodies are precursors of any portion of the thyroid parenchyma. Weller (1933), working with human embryos, reached essentially the same conclusion as Rogers, according to his estimate, the ultimobranchial bodies contribute as much as one third of the tissue of the definitive thyroid gland. Norris (1937) estimated that about one eighth to one sixth of the thyroid parenchyma is derived from these structures.

Possibly, according to Rogers and also to Godwin (1937, 1939), the strongly determined median thyroid cords may induce the less strongly determined ultimobranchial bodies to develop into a greater amount of thyroid parenchyma than is the case when the two structures remain separate—as occasionally they are observed to do. Recently Van Dyke (1944) explored further the theoretical and clinical implications of the problem of embryonic potency and determination. Ultimobranchial bodies lacking in inherent thyroid-forming potentialities may be induced by embryonic tissue to become transformed into thyroid-like tissue during embryonic development. Postnatally, however, the follicles so formed may undergo another transformation into cysts lined by squamous epithelium. Van Dyke believes that these cysts arise after birth in response to underactivity or an atrophic state of the thyroid parenchyma. Certain glandlike cells produced by the epithelium of the cysts develop into highly vascular, compensating thyroid cyst adenomata in atrophic glands.

Whatever the future course of investigations on the fate of the ultimobranchial bodies in embryology and after birth, it has been definitely established that these derivatives of the fourth branchial pouch complex (Kingsbury) may frequently become incorporated, to a

greater or lesser extent, within the expanding lateral wings of the developing thyroid gland

Kingsbury (1939) and Godwin (1940) believe (as did Grosser) that such fusion of the lateral thyroid anlage and the median thyroid anlage is followed only by retrogression of the lateral cell masses, or ultimobranchial bodies. At most, these cell masses may persist, as Van Dyke also thinks, to give rise ultimately to cysts. It is our belief that, should this theory be confirmed eventually, here indeed one would encounter an astoundingly broad embryological basis for future pathological developments — as if the destiny of the ultimobranchial bodies were no less or no more than to increase the chances of the formation of embryonic rests and the ultimate production of cancerous lesions as well as cysts.

ABERRANT (ECTOPIC) THYROID TISSUE

Schrager (1906) first proposed the term *aberrant thyroid*, which he defined as a mass of tissue having the structure of a normal or pathological thyroid gland and situated at some definite distance from the normal thyroid with which it has no connection whatsoever. According to Schrager, the condition was first recognized by von Haller in 1779, the first adequate description being published by Porta in 1849. Some authors state that aberrant thyroids are rare, although Gruber (1876) found that aberrant thyroid tissue occurs in 10 per cent of all cases in which autopsy material receives careful examination. What the actual incidence of such anomalies may be remains uncertain.

In embryonic development, during the descent of the gland rudiment minute portions (cell masses) of the thyroid tissue proper become detached. These glandular cell masses (1) may be deposited anywhere along the course of the thyroglossal tract from the foramen cecum to the thyroid gland, (2) may remain adherent to the aorta or its main branches as the heart and the great vessels separate from the thyroid gland during the development of the embryonic neck, and so give rise to aberrant thyroids in the mediastinum, (3) after being displaced, may be transported to distant sites as embryonic rests, (4) may persist as inclusions of fetal parenchyma (non differentiated masses or fetal follicles) within the thyroid gland proper, perhaps eventually to produce fetal adenomas and other types of tumors.

In rare instances, the entire thyroid gland may come to lie within the thoracic cavity, this anomaly must be distinguished from goiter plongeant, which is not the result of a developmental defect. In other rare instances, the backward migration may be prevented by the precocious development of the hyoid bone, so that the thyroid is finally represented only by a mass of tissue above the hyoid. Or, again, the downgrowth of the thyroglossal tract may be but partially interfered with by the anomalous development of the anlagen of the thyroid and the hyoid, thus thyroid tissue may come to lie above as well as below the hyoid, behind the hyoid bone, in front of the bone, or even in the body of the bone.

Aberrant thyroids may undergo any of the pathologic changes to which normally situated thyroids are susceptible. Thus, any variety of goiter may arise from such ectopic thyroid tissue. Colloid swelling, hyperplasia and neoplasia are among the possible developments. The marked tendency of aberrant thyroids to undergo changes leading to malignancy necessitates a clear understanding of the origin and nature of such tumors.

Distinction Between 'True' and 'False' Aberrant Thyroids Goitrous enlargement of portions of the normally situated, definitive thyroid gland may lead to the extension of glandular tissue into various abnormal locations: intrathoracic or substernal, subclavicular, retrotracheal, retrolaryngeal, circular (entirely surrounding the trachea). Such abnormally situated glandular tissue constitutes what is known as false aberrant thyroids or goiters. False goitrous tumors are usually found to be attached at least by a band of glandular or fibrous tissue to the gland of which it is a direct outgrowth. If no definite connection can be found between the ectopic nodule or tumor, the growth is assumed to be a true aberrant goiter. True aberrant thyroids develop only from embryonic deposit of thyroid tissue, cell masses being separated from the main mass of the growing gland and later being carried to various sites or being left as embryonic rests somewhere along the course of the thyroglossal strand.

Locations of Aberrant Thyroids Aberrant thyroids most frequently occur at the base of the tongue (lingual thyroid) and in the lateral cervical region (lateral aberrant thyroids). Thyroid tissue has also been reported as being present in the following locations: inside tongue (intralingual thyroid), below the tongue and above mylohyoid

muscle (sublingual thyroid), in the posterior wall of the pharynx (nasopharyngeal thyroid), in the posterior triangles of the neck, in the submaxillary triangle, in the supraclavicular fossae, in front of the

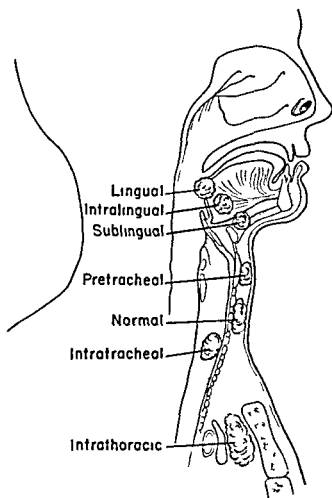


Fig 7 Usual position of aberrant (ectopic) thyroid tissue

larynx (prelaryngeal thyroid), within the trachea (intratracheal, thyroid), within the larynx (intralaryngeal thyroid) within the esophagus (intraesophageal thyroid), behind the trachea or larynx (retrotracheal and retrolaryngeal thyroids, such growths as a rule being false aberrant goiters, however), within the mediastinum (intrathoracic goiter), at times within the pleura or even the pericardium. Aberrant thyroids in the ovaries are known as *strumata ovarii*, or

ovarian strumas (ovarian thyroids or goiters) Exceptionally the osseous system is involved long bones, skull

OTHER DEVELOPMENTAL ANOMALIES

Absence of the Thyroid Gland In extraordinary instances, failure of the thyroid anlage to develop results in complete absence of the gland No thyroid tissue at all may be present except, possibly, ectopic or aberrant tissue, such as lingual thyroid tissue (Wells), or thyroid tissue located in an epithelial cyst at the base of the tongue (Aschoff), or possibly elsewhere In Wells case, even the lingual thyroid was hypoplastic

Absence of One Lobe When the thyroid anlage fails to undergo bifurcation during embryogenesis of the gland, one lobe is absent The right lobe is more frequently absent than the left lobe

Absence of the Isthmus At times the isthmus is completely absorbed in fetal life, so that the two lateral lobes are isolated

Congenital Hypertrophy Cases of congenital hypertrophy have been recorded, the overgrowth being apparently the cause of death of the fetus or newborn infant

PYRAMIDAL PROCESS (LOBE)

When the isthmial band is partly absorbed, the unabsorbed portion may give rise to the pyramidal process or lobe, the developmental anomaly of most frequent occurrence in man The pyramidal process may be connected with either lateral lobe, more often with the left In some cases, the thyroglossal tract has divided in two during fetal life so that two pyramidal processes are formed, one on each side

At about the fifth week of fetal life, the hyoid anlage appears dorsal to the already developing thyroid anlage The thyroid strand fuses with the periosteum of the hyoid and when the bone rotates to assume the adult position, the thyroid strand is drawn posteriorly This fusion with the periosteum results in a definite break in the thyroid strand and may lead to the attachment of the pyramidal process to the hyoid

The thyroid tissue may or may not be evenly distributed through the pyramidal lobe whose structure varies from that of an almost wholly glandular lobe to that of a scarcely detectable fibrous strand often containing islands of thyroid tissue Two explanations have been

proposed for this variation in quantity and distribution of active thyroid tissue in the pyramidal lobe (1) thyroid epithelium outside the gland proper in varying degrees exhibits a tendency to regress, and (2) growth of muscle, cartilage and fascia around the thyroid strand in varying degrees compresses it so that its development is hindered wholly or in part. Muscle fibers largely derived from the thyrohyoid may occasionally become intimately involved in the structure of the pyramidal process, the muscular tissue then being known as the levator glandulae thyroideae.

Beilby and McClintock found that 26 out of 28 thyroids possessed either a definite pyramidal lobe or a fibrous cord containing varying amounts of thyroid tissue and extending from the thyroid to the hyoid bone. In 73 per cent of the 26 thyroids having a pyramidal lobe, thyroid tissue was grossly demonstrable, the other pyramidal lobes being represented by a definite fibrous cord which presumably contained at least a minimum of thyroid tissue. It is generally stated that the incidence of the anomaly found in anatomical studies is about 40 per cent.

Hence the high percentage (92 per cent) of occurrences reported by Beilby and McClintock would seem to result from their inclusion of instances in which merely a fibrous cord or islands of thyroid tissue were found. Grüber (1876) reported an incidence of 40 per cent in his specimens. The incidence as given by other investigators is as follows, in terms of percentage of positive findings: Marshall (1895), 43, Joll (1932), 75, and Berlin (1934), 35.

ANOMALIES IN RELATION TO THE HYOID BONE

Various anomalous relationships between the hyoid bone and the thyroid arise from the mode of embryonic development of the bone and the gland. In the very early stages of the embryo, the thyroid primordium grows downward in the midline through the region in which the hyoid later appears. Following the appearance of the bifurcation that leads to the formation of the isthmus and lateral lobes of the gland, the hyoid develops inward from right to left, to fuse at the midline. Hence there are three obvious developmental possibilities, the realization of any one of which depends upon the normal or abnormal nature of the growth of the hyoid and the thyroid. (1) the thyroglossal tract may develop, as it normally does, in front of the

hyoid, i.e., ventral to the bone, (2) it may develop behind the hyoid, or (3) the tract may even extend into the body of the bone. The surgeon who has to deal with a thyroglossal duct that is fistulous must bear in mind these various possibilities. Occasionally, a thyroglossal fistula will not yield to surgery unless the hyoid has been partially resected (or at least thoroughly curetted). The explanation may be that the canal extends through the hyoid bone which, during embryonic development, underwent anomalous growth and completely surrounded the duct. Embryonic rests may be enclosed within the body of the hyoid and tumors may eventually arise from them.

The precocious development of the hyoid may interfere with the normal descent of the thyroid gland rudiment, which then may give rise to a mass of functional thyroid tissue situated between the base of the tongue and the hyoid. Other aberrant thyroid tissue may or may not be present.

The intimate connection established between the thyroglossal duct and the periosteum of the hyoid bone during the second month of fetal life accounts for the frequently observed attachment of the pyramidal lobe to the hyoid.

THYROGLOSSAL DUCT ANOMALIES

At times the thyroglossal duct may persist in whole or in part, so that any (or all) of the following types of lesions may result: (1) thyroglossal cysts, (2) thyroglossal fistulae, and (3) solid tumors, which may be either benign or malignant. The location of such lesions depends upon the relation of the developing thyroglossal tract to the embryonic hyoid bone (see page 39) and upon possible adherence of portions of the thyroid anlage to the downward migrating embryonic heart and great blood vessels. In rare instances, the thyroglossal tract exhibits lateral branching.

THYROGLOSSAL CYSTS AND FISTULAE

The thyroglossal duct may exceptionally extend as a continuous canal from the foramen cecum to the isthmus of the thyroid and, very rarely, on beyond, into the mediastinum and perhaps even as far as the aorta. Usually, the course of the thyroglossal tract is from the foramen cecum, through the posterior part of the tongue, along the lingual raphe, and in front of, behind, or through the hyoid bone. Usually the tract passes through the incisura of the thyroid cartilage, in front

of which it grows downward. Often intimate adhesions will be found between the tract and the thyrocricoid membrane.

Most commonly, only part of the persistent thyroglossal tract is patent, the lower portion more frequently than the upper portion.

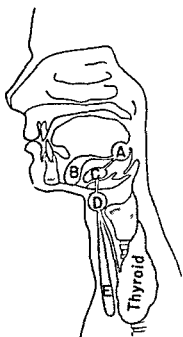


Fig. 8. Usual position of thyroglossal cysts. (A) Lingual, (B) Sublingual, (C) Suprahyoid, (D) Infrahyoid, (E) Subthyroid.

Embryologically, the upper portion is older, its atrophy and obliteration beginning somewhat earlier than in the case of the lower portion. Furthermore, less pressure is exerted upon the lower portion from the outside, whereas collapse of the duct passing through the base of the tongue and obliteration of the part above the hyoid are promoted by the action of the muscles of the tongue. Consequently, the most frequent location of a thyroglossal cyst is just below the hyoid bone, although such cysts also occur beneath the foramen cecum (as well as below the thyroid gland). Because of anomalous development during embryonic life, cysts may be found behind the hyoid or even within

it. Thyroglossal cysts may be single or multilocular. Cases have been reported in which such cysts were found in the floor of the mouth as forms of ranula. In thyroid aplasia of cretins and in unilateral aplasia of adults, small multilocular cystic tumors frequently occur along the upper course of the thyroglossal tract, i.e., in the region of the lingual duct.

The thyroglossal duct, an epithelial tube, may be lined with (a) squamous epithelium arising from the primitive mouth, or (b) ciliated columnar epithelium originating from the primitive pharynx. There is no connection or physiological relation between either of these linings and the thyroid gland despite the fact that the median primordium of the thyroid develops around the duct. Pharyngeal tissue may be pulled downward during the growth of the thyroglossal tract, so that

retention cysts later develop. When severance of the connection between the thyroglossal duct and the foramen cecum leads to cyst formation mucous secretion from the lining cells and mucous glands accumulates in the cyst and tends to prevent its obliteration. The cyst may have a fistulous opening into the pharynx at the foramen cecum as a result of persistence of the lumen of the thyroglossal duct. The foramen cecum provides a readily developed outlet for secretion in the upper portion of the canal (lingual duct). Secretion in the deeper portion (thyroid duct) is much more likely to be retained and cause the development of median cysts.

Lateral ducts from salivary gland acini were found by Bochdalek to open into some persistent thyroglossal ducts (lingual ducts).

Infection of a thyroglossal cyst may result in suppuration and the production of a fistulous opening at the foramen cecum, occasionally a suppurating cyst may rupture to the exterior, but true external thyroglossal fistulae do not develop because the developing thyroglossal tract does not make contact with the skin.

In a total of approximately 3 800 surgical thyroid specimens Frantz and co workers (1942) found 39 thyroglossal cysts.

INTRATHORACIC GOITER

Although intrathoracic or substernal goiter was first described anatomically as far back as 1749 by Haller and clinically by Lingl in 1830 it was not generally recognized before 1899, when Schieff demonstrated the value of roentgenogram in its diagnosis.

The present day classification of intrathoracic goiter is vague. Descriptive terms such as substernal, retrosternal, and subclavicular add to the confusion. We would suggest classifying all of them as intrathoracic. Further explicit description could be obtained by expressing to what degree the thyroid is submerged in the thoracic cage. For instance, if one third of a lobe were intrathoracic it might be called intrathoracic goiter first degree. If two thirds of the goiter were intrathoracic it might be termed second degree. This would facilitate reporting these cases and give us a better statistical approach as to their respective occurrence.

Substernal goiters may be partial or complete, fixed or mobile. Such nomenclature as wandering goiter, spring goiter, and goiter mobile has been applied to the mobile type of substernal goiter.

Most cases are the result of downward protrusion of the thyroid as a nodule in nodular goiter extends its growth from a lower pole of the gland. The overlying muscular structure (especially the pre thyroid muscle) tends to direct the growth downward pressure being exerted by contractions during swallowing. Little resistance is offered by the loose alveolar tissue in the upper mediastinum. Less frequently, intrathoracic goiters take rise from diffuse colloid goiter. Only in very rare instances are intrathoracic tumors the result of growth from true aberrant thyroid tissue. In true aberrant intrathoracic goiter, no connection (strand or cord of fibrous or thyroid tissue) links the tumor with the definitive thyroid. Even if no such connection is detectable the thyroid tissue giving rise to the tumor may have originated from the thyroid gland proper by benign metastasis or perhaps, in some cases, a connecting strand was present but eventually was severed with continued descent of the tumor into the thoracic cage.

According to Means (1938), approximately 12 to 15 per cent of goiters are substernal whereas less than one per cent are (completely) intrathoracic. That the partially substernal goiter is not an unusual condition is readily apparent from our own statistics. In our group of 15,000 thyroidectomies performed in the past 25 years (1923 to 1948) 15 per cent fell into this category. Completely substernal or intrathoracic goiters, on the other hand, are indeed extremely infrequent. It is difficult to estimate from the literature the true incidence of this condition, as every surgeon differs in his definition of intrathoracic by degree.

In our last personal series of 1,000 thyroidectomies only three were completely intrathoracic. It is of interest that all three cases proved to be adenomas thus further confirming the general belief that intrathoracic goiters generally originate from adenomas or adenomatous goiters.

One of the cases of intrathoracic goiter was an adenoma which was continuous with the left lobe of the thyroid and which was removed through a low collar incision of the neck. This adenoma measured 10 cm. in length and 7 cm. in diameter.

In the second case, the goiter was removed by splitting the sternum. Although it was not as large as in the first case, it was very adherent to the surrounding structures.

In the third case, which we are presenting in detail the goiter was

the largest yet reported and was entirely intrathoracic, being connected to the trachea in the neck by only a thin fibrous band. In fact we think it might be considered an ectopic or aberrant thyroid. When removed it measured 15 cm. in length, 11 cm. in diameter and 8 cm. in depth, the largest intrathoracic goiter yet reported to our knowledge.

E. F., a male, aged 49, weight 196 lbs., was seen at the clinic on May 15, 1943. He complained of dyspnea, occasional pains in the back and occasional epigastric distress. There were no other symptoms. When first distressed with dyspnea a year previously, he had consulted a physician who had prescribed some pills. While under this treatment he lost 40 pounds in weight. He consulted another physician,

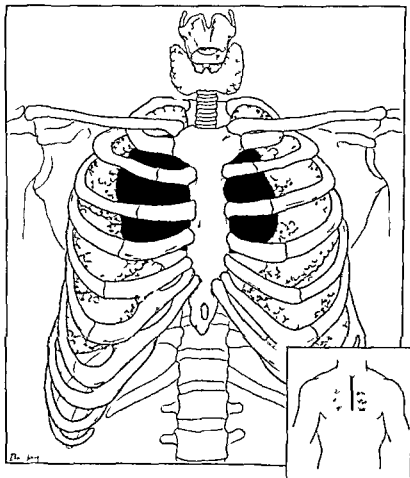


Fig 9 Intrathoracic goiter, third degree. Appearance of tumor within thorax. Insert shows incision of sternum.

who after examination advised x rays of the chest. Roentgenograms revealed a tumor mass. X ray treatments were then instituted. During this time he felt better and regained the 40 pounds in weight. Follow up roentgenograms, however, failed to show any regression of the tumor.

On examination at the DeCourcy Clinic, the patient, a barrel chested individual, had a systolic blood pressure of 150, diastolic 100, pulse was 88, temperature 98° F. Urinalysis revealed specific gravity of 1.010, acid reaction, negative chemically. On microscopic examination, there was an occasional epithelial cell. Examination of blood



Fig 10 Anteroposterior view showing deviation of trachea



Fig 11 Lateral view

showed hemoglobin of 88 per cent, red count of 4,580,000 and white count of 7,000. Differential was essentially normal. Wassermann and Kahn tests were negative.

X ray of the chest showed a thickened pleura over the right lung. Lung fields and pleura were otherwise clear. A very large tumor mass could be visualized in the region of the mediastinum extending both to the right and left. This suggested an aneurysm of the aorta, the heart outline was not enlarged.

X ray of the gallbladder was taken on May 21st. The roentgenologist reported that the gallbladder was not visualized and advised another examination. X ray of front and side views of chest taken on this date showed a large, well circumscribed shadow of increased density in the upper anteriomedistinum, which displaced the trachea back



Fig 12A Tumor after shrinkage 13.5 by 11 by 8 cm



Fig 12B Tumor showing tracheal groove and previous attachment to pericardium



Fig 12C Tumor halved longitudinally

ward and to the right. It appeared to be continuous with the arch of the aorta and therefore suggested the presence of a large aortic aneurysm. The heart outline was not enlarged.

On June 12th, further x ray of chest showed the same findings as previously described. There were no changes.

Repeated fluoroscopic examinations, however, failed to convince us of the diagnosis of aneurysm. More deep therapy was applied but there was no regression.

Believing that we might be dealing with an intrathoracic goiter, 10 drops of Lugol's solution were given three times daily for ten days. The patient entered the hospital on June 30, 1943. The thyroid in the neck was not palpable.

On July 3, 1943, operation was performed under nitrous oxide and oxygen anesthesia. A low collar incision was made over the neck, which was very short, the thyroid cartilage being only one inch above the sternal notch. The left lobe of the thyroid could not be found and the right lobe was very small and flattened against the trachea. No nodules were palpable.

As the finger was inserted beneath the sternum, the upper border of the tumor could be palpated. The sternum was then split lengthwise in its middle portion down to the xiphoid. The electric circular saw and chisel and hammer were used. Where the halves of the sternum were separated, an exposure of about $2\frac{1}{2}$ to 3 inches was obtainable. The tumor was seen lying beneath in the midline with the pleura thickened and pushed downward by the tumor.

Enucleation was started and it was thought that an easy removal would be effected, however the adhesions became very dense where attached to the pericardium. Bleeding became profuse and necessitated stopping the operation and packing about the mass with hot moist packs. A transfusion was added to the intravenous glucose solution and the patient was returned to bed.

Twenty four hours later the patient was sitting up in bed talking. *Active bleeding had stopped*, pulse was 90 and of good volume, respirations were 28, temperature was 102°F per rectum. Twelve hours later (36 hours postoperatively) the temperature rose to 108°F . Respirations became quickened and labored, the pulse rapid, and the patient expired.

At autopsy the thorax was opened in the usual manner, by extending the midline incision and making a horizontal incision from the shoulders to the superior portion of the operative incision. Behind the sternum and ribs, there was an encapsulated tumor mass, about 15 cm by 11 cm by 8 cm, situated in front and to the left of the trachea which was compressed. The lateral and anterior sides of the mass were closely related to the lungs and pleuras. The lateral and inferior

as big as walnuts. A suprahyoid thyroid nodule may be present in association with a lingual thyroid (at the foramen cecum) or a lingual thyroid may be present along with a normally situated and apparently normal thyroid gland. Parathyroid nodules have been found in fibrous tissue connected with the ventral surface of a lingual thyroid. Their

incidence may possibly be the same in both sexes although statistical studies are lacking. Symptom producing hypertrophy is of course much more frequently reported in the female.

Montgomery (1936) collected a series of 141 cases and noted that some two thirds to three quarters of the cases with symptom producing thyroid gland nodules at the base of tongue may be without a normally situated thyroid gland. Six of the 141 patients had associated accessory thyroid nodules in the neck. This author classified 85 cases according to the predominant histological structure of the lingual thyroids as follows: (1) apparently normal type of thyroid tissue, 55.3 per cent of cases;

(2) fetal or early type of thyroid tissue (hyperplastic form, tissue characteristic of early embryonic thyroid), 20 per cent; (3) possibly degenerative type of tissue, 9.4 per cent; and (4) definitely degenerative type of tissue, 15.3 per cent (the occurrence of calcium deposits being noted in some instances).

When the lingual thyroid is the only thyroid tissue present, the simplest explanation would seem to be that the anlage persisted at its site of origin in the very young embryo, backward migration possibly being prevented by the precocious development of the hyoid bone. Limited migration of the median primordium associated with deposit of a portion of the anlage at the base of the tongue may account for those instances in which a suprahyoid and a lingual thyroid coexist. Persistence of a fragment of the anlage at the foramen cecum and otherwise normal development and normal migration of the thyroid primordium may well be the embryologic history in those cases in



Fig. 16 Thyroglossal tumor of tongue. Note the large vessels on its surface. (From Joll C. A. *Diseases of the Thyroid Gland*. London: Wm. Heinemann Medical Books Ltd.)

which thyroid tissue is found at the base of the tongue and a normally located thyroid gland is also present. In the very rare instances in which thyroid tissue occurs within the tongue embryonic thyroid tissue may have been detached from the anlage and carried forward by the migration of the tuberculum impar to give rise to a fetal rest.

It is of clinical interest to note that symptoms of thyroid insufficiency may follow removal of a lingual thyroid when it is the only thyroid tissue present and that the tumor may recur postoperatively. Montgomery records 6 cases of postoperative recurrence among the 141 patients with lingual thyroid in his series. remarkably he was unable to find cases of lingual thyroid carcinoma in the female but several cases in the male all of these patients being past the age of 35 years.

LATERAL ABERRANT THYROID

Lateral aberrant thyroids occur as cystic tumors frequently papillomatous situated in the neck lateral to the normally located thyroid gland and at various distances from it. The attention of many investigators has been attracted by the marked tendency of lateral aberrant thyroids to become malignant growths, and recently interest in them has increased because new studies focusing on the problem of etiology, have provided weighty evidence that these tumors represent metastases from a primary tumor in the homolateral lobe of the gland proper rather than from embryonically displaced fragments of the thyroid anlage.

The term lateral aberrant thyroid was first suggested by Schrager (1906), who regarded these growths as the products of anomalous embryonic development — true ectopic thyroids from misplaced portions of the thyroid anlage. Previously however Low (1903) had pointed out the predominantly papillary nature of these tumors and their frequent association with similar tumors of the homolateral lobe of the thyroid. He stressed the slowness with which these aberrant thyroids grow and the infrequency of their metastasis to distant sites their invasion of other tissues tending to take place via the lymph channels. As has been pointed out in the discussion of the significance of the ultimobranchial bodies Grosser Kingsbury and other authors have long contended that the so-called lateral thyroid anlagen (ultimobranchial bodies) as a rule degenerate following their fusion with

the median anlage and probably disappear completely, this theory, together with the growing understanding of the peculiar structure of lateral aberrant thyroids, led to the belief that their (thyroid) tissues originate not from normal thyroid elements but from the ultimobranchial bodies — presumably representing tissues constitutionally inferior to that of the thyroid gland

As early as 1917, Wohl suggested that carcinoma in so-called lateral aberrant thyroids might actually represent metastasis from a primary tumor in the thyroid gland. Nevertheless most authorities continued to regard them as growths from embryonically misplaced thyroid tissue. Cattell, however, proceeded to modify the *fetal rest* theory. According to this author, lateral aberrant thyroids are intrinsically malignant because they arise from fetal rests, themselves derived from a degenerated lateral anlage (ultimobranchial body) on each side. Cattell further thought it probable that fetal rests from the same source are also the origin of the papillary tumors which are frequently present in the corresponding lobe of the thyroid along with lateral aberrant thyroids. Crile supported this explanation of the origin of coexistent lateral aberrant thyroid tumors and tumor of the homolateral lobe of the thyroid, but regarded the lateral aberrant thyroids as markedly *benign*.

Dunhill (1931) developed the theory of activated rests. Ordinary physiological stimuli frequently cause papillary change in tissue derived from the lateral anlagen, such tissue being constitutionally inferior to that derived from the median anlage, the inferior tissue (embryonic rests) may be situated either within or without the thyroid lobe. Van den Wildenberg went on to express the belief that the papillary cystadenomas so arising are precancerous, malignancy being induced by the increasing stimulation in thyroid insufficiency. Continuation of such stimulation, according to Greteman and Russum, cause minute rests, missed at the first operation, to grow into palpable tumors, the thyroid proper is frequently involved and should be explored for a similar tumor. Colin and Stewart (1940) expressed the belief that embryonic tumor cells may be split off from the ultimobranchial bodies (lateral component of the thyroid) either before or after fusion of these bodies with the median anlage, and thus the situation of a papillary tumor within or without the lateral lobe of the thyroid is determined. Coexistent primary tumors develop in the thyroid and side

of neck if this splitting off takes place both before and after fusion. To prevent recurrence, complete excision of the tumors is necessary, (Cohn and Stewart)

Lahey and associates (1940) remarked on the frequent coexistence of carcinoma in the thyroid proper and in lateral aberrant thyroids. Their interpretation is that the lateral tumor is the primary one, from which metastasis to the thyroid proper occurs. In this report, they state that in 18,600 goiter operations, there were 36 cases of carcinoma in the lateral aberrant thyroids, an incidence of approximately 0.2 per cent. Apparently including both benign and malignant tumors. Crile reported that the incidence of lateral aberrant thyroids is one such tumor per 1,000 goiter operations.

Frantz and co-workers (1942) recorded 30 cases of lateral aberrant thyroids (and 6 cases of median aberrant thyroid tumor) in a total of approximately 3,800 surgical thyroid specimens (1924-1941). According to these authors, true lateral aberrant thyroids may have different embryological origins. In most instances, lateral aberrant thyroids are derived from the lateral thyroid body and cell cords from the lateral cornu of the median anlage which has been fused together but subsequently have become detached from the main part of the median anlage. In cases of lingual thyroid, however, any lateral aberrant thyroid tissue would be derived entirely from the lateral thyroid — the ultimobranchial bodies — and would probably, although not necessarily, be associated with the parathyroid arising from the fourth pharyngeal pouch. This explanation is in accord with the views of Weller (1933) who remarked that occasionally, in congenital cretinism, descent of the thyroid below the hyoid may not have taken place but isolated small masses of thyroid tissue are found low in the neck. Weller believes that such anomalies may be taken as evidence of the differentiation of the fourth pouch material (ultimobranchial bodies) into thyroid tissue.

Frantz et al. observe that it is always difficult and sometimes impossible to differentiate between lateral aberrant thyroid tumors and metastases to the cervical lymph nodes from carcinoma of the thyroid. They believe that when multiple small foci are found in a lymph node, one is dealing with metastases rather than multiple aberrant thyroids. They consider metastases only those tumors whose groups of cells lie scattered in a structure which has the architecture of a lymph node.

(marginal sinus sinusoids, lymph follicles) All of these tumors should be considered potentially malignant, treated radically, and followed with care

According to the notable report of King and Pemberton (1912), lateral aberrant thyroid masses are in reality metastases from a carcinoma of similar structure in the thyroid gland itself, papillary cystic thyroid tissue is often metastatic from a primary tumor of identical type in the homolateral lobe of the thyroid Thus these workers record confirmation of the suggestion of Wohl (1917) They carefully studied 51 cases of malignant aberrant thyroid lesions in the lateral cervical regions of which 31 were associated with carcinoma of the homolateral thyroid lobe, established by microscopic examination, no examination being made of the other 20 thyroid glands In 19 cases, specimens from the thyroid gland and the lateral cervical masses were proved to be identical in type

King and Pemberton also cite 15 cases in which the diagnosis was definitely papillary carcinoma of the thyroid with metastases to the cervical lymph nodes These cases differed from the first series only in the relative degree of prominence of the tumor as indicated by the laboratory findings and the clinical history In both series of cases, the lateral metastases contained lymphoid tissue in 60 per cent of the specimens

King and Pemberton explain the presence of so-called benign lateral aberrant thyroid tumors as follows Adenomatous masses are pinched off from a large nodular goiter by muscles and other surrounding structures drift laterally or upward through the lymph channels, and become implanted as aberrant thyroid tissue Large adenomas found in the thorax and completely separated from the primary tumor within the thyroid arise similarly These authors conclude that, even if a gross tumor of the thyroid is not evident at operation, lateral aberrant thyroid tumors are not adequately treated until the homolateral lobe of the thyroid has been removed

More recently, Clay and Blackman (1944) have stated that lesions long known as lateral aberrant cervical thyroids should be considered as metastases in the cervical lymph nodes from primary carcinomas of the homolateral lobe of the thyroid — until satisfactory evidence to the contrary is adduced They stress the point that the thyroid should be explored and at least the corresponding lobe removed when such lateral tumors are present, even though the primary tumor (in the

thyroid) may not be palpable. Possible development of a similar lesion in the other lobe must be kept in mind. Clay and Blackman feel that surgical removal of the primary lesion and the first metastases may well prevent spread to the lungs, bones and other sites, extension of such growths being remarkably slow.

Such tumors may look histologically benign, but, nevertheless may be malignant. Further, random sections of a lateral cervical thyroid tumor may not reveal the architecture of the residual lymph node, the node is frequently destroyed by a growing metastasis.

BENIGN METASTASIZING COLLOID GOITER

We believe that the problem of the origin of lateral aberrant thyroid tumors is closely related to the problem of so-called 'benign' metastasizing colloid goiter. In fact, the two problems may turn out to be fundamentally the same, involving the striking capacity for independent growth shown by thyroid tissue. Dissociated tissue alveoli tend to grow rather than to regress (Ewing). In fact, a number of reports indicate the possibility that even the apparently normal thyroid may show metastasis. A tumor removed from the inferior maxilla was found to be composed of normal thyroid tissue, according to Riedel, and local recurrence was observed after 10 years, the thyroid gland undergoing no observable change the meanwhile. A perforating tumor of the skull, similarly composed of normal thyroid tissue, was excised by Oderfeld and Steinhaus, no enlargement of the thyroid was noted and no accessory thyroids were found. We consider it possible that these tumors may have arisen from embryonic rests, the interpretation placed on such growths seems to depend upon the opinion of the observer, sufficient evidence for a satisfactory explanation being obviously lacking.

Connheim (1876) first drew attention to so called benign metastasizing colloid goiter, since then, more than 100 cases have been recorded. Some authors have stated that the tumors arise, in these cases, from aberrant portions of the thyroid anlage, i.e., are growths from embryonic rests. Possibly, a certain proportion of the growths do so originate. Nevertheless, in other instances — especially when the osseous system is extensively involved — the factor of malignancy masked by extremely slow spread and slow growth must be considered. Boyd (1943) recently stated unequivocally that clear evidence of

malignancy will eventually be forthcoming in all cases of so called benign metastases of simple colloid goiter

STRUMA OVARII — OVARIAN GOITER

Although struma ovarii is a comparatively rare type of aberrant thyroid it is not only of great embryological and pathological interest but also of vital importance in a considerable percentage of the cases that are encountered in the clinic. In 1910 Emge collected 150 cases from the literature since 1899 when Gottschalk recorded the first case of strumal tumor of the ovary as *folliculoma malignum ovarii*. Gusberg and Danforth (1911) noted that 31 additional case reports had appeared since Emge's survey. We believe that the increasing knowledge concerning this condition will result in an increase in cases reported annually. Undoubtedly many cases escape diagnosis. The observed incidence of thyroid tissue found in dermoid cysts for instance varies from 1.5 to 28.5 per cent thus both technique and criteria of diagnosis obviously must affect the determinations presented in the literature. Gusberg and Danforth in their recent analysis of cases found that 2.7 per cent of 297 ovarian teratoma of all types examined during a twenty year period were struma ovarii. In addition a number of thyroid rests were observed the diagnosis of struma ovarii being confined to those tumors which contained significant percentages of thyroid tissue. Unavoidably perhaps different observers will continue to differ concerning just what proportion of thyroid tissue in such tumors must be regarded as significant.

It has been definitely established that struma ovarii does not represent mere colloid degeneration of cysts arising from one or another of the numerous varieties of tubular structures within the ovary. Microscopic studies have shown that the differential staining qualities of the colloid and the morphologic stigmata of the parenchyma are such as to prove the presence of aberrant thyroid tissue in struma ovarii.

In 1912 Trapl suggested that strumal tumor of the ovary may function vicariously as thyroid. Subsequent research has left no doubt that struma ovarii can contribute to thyrotoxicosis. This remarkable capacity distinguishes ovarian struma among all ovarian growths and as Gusberg and Danforth have noted removes it from the category of the simple pathologic curiosity. These workers point out that of the 31 ovarian strumata recorded in the literature from 1910 to 1911 8

were said to have been accompanied by thyrotoxicosis. In at least 5 of these 8 cases, there was coincident enlargement of the thyroid. The thyrotoxic symptoms of 3 patients were relieved by oophorectomy alone, previous subtotal thyroidectomy failed to alleviate the hyperthyroidism in 2 patients.

Nevertheless, basing our conclusions on the data available in the literature, we must assume that there are fundamental morphologic as well as physiologic differences between ovarian thyroid tissue and normally situated thyroid tissue. These differences would seem to bear directly upon the problem of the (embryologic) origin of the ectopic tissue. In most instances in which relief of thyrotoxic symptoms has been observed to follow removal of the tumor, subsequent microscopic examination of the ovarian sections has not revealed the stigmata of hyperthyroidism. The thyroid tissue seldom shows evidence of hyperplastic changes in these cases. That is, the histologic changes do not parallel the level of toxicosis. Nor does the iodine storage correspond to the physiologic or morphologic changes (Emge). Masson and Mueller (1933) determined the iodine content of the thyroid tissue in three ovarian tumors, in terms of iodine content per cent of dry weight the values obtained were 0.105, 9.031, and 0.011. The majority of ovarian thyroids store very little iodine (Emge).

The growth characteristics of ovarian strumas are of signal importance as respects both embryological (etiologic) and surgical considerations. Most such strumas are believed to be benign tumors having orderly growth characteristics, but approximately 5 to 6 per cent have been reported to manifest metastatic growth habits, although the more severe types of hyperplasia are rare. In the majority of instances ovarian strumas show a tendency to develop into a colloid goiter rather than to maintain hyperplastic activity (Emge). Metastases from a malignant struma ovarii are generally restricted to the abdominal viscera and are superficial rather than invasive. Hence, their behavior is unlike that of metastatic neoplasms of the thyroid gland proper. Nevertheless, at least two metastases to bone have been recorded and the assumption of malignant tendencies in other cases resulted in death in about fifty per cent of the patients. A patient may survive for years even though multiple aberrant thyroids are present, in one instance, death did not occur until 18½ years after operation with known metastases still present (Morgen).

Various authors have proposed classifications of ovarian strumas according to hyperplastic activity and morphologic structure (microfollicular, macrofollicular). Such attempts have not met with general approval because functional activity and morphologic nature as a rule are not related variables. Within the same tumor, different degrees of hyperplastic activity may be observed. The quantity of thyroid tissue present is not an index of functional activity although of course a certain minimum of functional tissue must develop before symptoms of thyrotoxicosis appear.

Most authorities apply the term *teratoma* to both cystic and solid ovarian tumors. In the cystic teratoma, as a rule all three fetal layers are recognizable and are arranged in a more or less orderly manner but the structures arising from the ectoderm may be (and usually are) predominant. All three germinal layers are present in the solid teratoma also, these tissues, however, are mingled indiscriminately, and the histological findings usually suggest an embryonic development. It is generally accepted that about 80 per cent of ovarian tumors are cystic whereas 20 per cent are solid, but mixed tumors are encountered. The coexistence of a hyperplastic strumal tumor and a granulosa cell tumor has been reported only twice (Murray, Dockerty and Pemberton Frankl). We are of the opinion that the more painstaking the microscopic examination of sections from ovarian tumors, the more frequently the presence of thyroid tissue will be disclosed not only in such tumors but in others in which the occurrence of thyroid tissue is generally believed to be very rare. The chance avoidance of thyroid tissue in the sectioning of large ovarian tumors has been emphasized as clinically important by Gusberg and Danforth (1944), functioning ovarian strumas may escape diagnosis, especially when the symptoms of hyperthyroidism are mild. Dermoid cysts constitute about 10 per cent of the cystic tumors, but even in these the precise incidence of thyroid tissue is as yet uncertain. In the literature, the point has been made that the dermoid tumor is benign whereas the teratoma is malignant, recent reports do not support this belief, which — if true — would be of clinical interest.

Indeed the fact that a certain percentage of ovarian strumas can give rise to malignant metastases makes obvious the necessity of a careful study of the abdominal cavity at the time of operation to remove these tumors. Annual bone surveys should subsequently be

made. Further clinical considerations arise when thyrotoxicosis accompanies coexistent enlargement of the thyroid and an ovarian tumor, the enlargement of the gland may be such as to indicate thyroidectomy but at the same time the possibility of a functioning struma ovarii must be recognized. Weighing of the factors involved may prevent needless removal of the thyroid.

The behavior of metastasizing thyroid neoplasms is evidence against the hypothesis that ovarian strumas represent thyroid metastases into the ovary. And we do not regard as plausible the suggestion that such tumors arise from some ill understood ovogenic development unorganized in nature. The most likely explanation of their origin would seem to be embryologic, i.e., it appears probable that an ovarian struma develops from an embryonic rest whose mass of cells became detached from the thyroid anlage and was carried to a distant site (the ovary) during early fetal life. So-called pure ovarian strumas have been described occasionally, but in common with most authors we believe that close microscopic scrutiny of such specimens would disclose the presence of at least a minimum of elements from the embryonic sources said to be unrepresented. In any case, whether the struma ovarii clearly involves all three germ layers in a totipotent development or appears to be constituted purely of thyroid tissue, these growths must, for the present at least, be regarded as regional teratomas — and of embryonic origin.

FETAL ADENOMA

According to Wolfler, fetal adenoma must be attributed to growth from superfluous embryonal thyroid epithelium to be found throughout the gland. With Langhans, he theorized that all the ordinary thyroid epithelial tumors take rise from persistently embryonal cell masses, obscure disorders of development being involved in the origin and distribution of these cell groups within or without the thyroid gland proper. Thus they account for gelatinous adenoma (colloid goiter), adenocarcinoma, and carcinoma as well as fetal adenoma. But Ewing has observed that only in fetal adenoma can embryonal cell groups be definitely implicated. Considerable histologic evidence as well as the fact that a lengthy period of benign overgrowth precedes the development of malignant tumors would seem to necessitate the assumption that many

adenomas, adenocarcinomas and carcinomas may spring from adult follicles

Some atypical, rapidly growing sarcomas may, like fetal adenomas, take rise from embryonal epithelium. Fetal adenoma appears early, usually becoming a definite tumor sometime before the twentieth year of life. Papillary fetal adenoma develops when small cysts are invaded by epithelium growing in low papillary form. There is no doubt that some adenocarcinomas, carcinomas and sarcomas arise from fetal adenoma.

TIME OF ORIGIN OF FUNCTION OF THYROID

Embryologists have stressed the significance of hormones as morphogenetic factors in the developing fetus. Therefore, as Gorbman and Evans (1943) have observed, the determination of the embryonic stage at which thyroid tissue becomes functional is of great interest. Functional fetal tissue, moreover, must be regarded as a clinical consideration in the frequent cases of hyperthyroidism in pregnancy. Gorbman and Evans injected radioactive iodine into female rats at a known stage of pregnancy and later, by the radioautograph technique, measured the extent of iodine storage in the developing tissues of the fetal thyroid. Fetuses less than 19 days old showed almost no storage of iodine in their thyroid tissue, but considerable storage was detected in 21 day old fetuses, functional ability therefore apparently beginning on the eighteenth or nineteenth day of embryonic life. These authors interpret their data as indicating that, in this mammal at least, thyroid function does not begin until 90 per cent of the intra uterine life is completed and probably starts at the time of first differentiation of the follicles within the lumina. The follicular differentiation first appears in the peripheral portions of the thyroid and gradually extends into deeper tissues. The observations of Gorbman and Evans support the view that physiological differentiation depends upon, or immediately follows, morphological differentiation.

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CHAPTER IV

ANATOMY, HISTOLOGY, AND CYTOLOGY OF THE THYROID

GROSS ANATOMY

THE THYROID, an unpaired, ductless gland, is situated at the front and sides of the lower part of the neck — opposite the second, third and fourth tracheal cartilages, i.e., at about the level of the fifth, sixth and seventh cervical vertebrae. Some apparently normal glands may extend from the level of the first tracheal cartilage as far as the level of the fifth or even the sixth tracheal cartilage. A right lobe is connected across the median plane to a left lobe by a thin band of tissue the isthmus, which usually covers the second, third and fourth rings of the trachea. Each lobe is roughly conical in shape, with the apex directed laterally upward, and is approximately 5 cm long and some 2 cm in thickness, the width of the base being about 3 cm. Generally the isthmus measures approximately 1.25 cm transversely and about the same vertically, it does, however, show many variations and in some 10 per cent of cases, is altogether lacking. There are usually two blunt poles — a superior and an inferior on each lobe, the inferior pole is less frequently absent than is the superior one. In less than one per cent of cases, one lateral lobe may be absent.

A pyramidal lobe is frequently present (see page 38), often extending from the upper part of the isthmus to the hyoid bone. In many other instances, the pyramidal lobe is connected with the adjacent portion of one lobe or the other, more commonly the left. It may or may not be attached to the other portions of the thyroid and may be divided into two or more parts. Accessory thyroid glands (page 35) are of frequent occurrence.

Weight at Birth. The weight of the thyroid gland in the newborn varies according to the region (and the availability of iodine). In a non goitrous region (Wichita, Kansas), Hellwig found that the weight of the gland in the newborn averaged 1.2 Gm. In Minneapolis (moderately goitrous region), Rice recorded an average weight of

the thyroid gland at birth of 1.5 Gm. Jaffé found 1.6 Gm. to be the average weight of the gland in the newborn at Chicago, also in a moderately goitrous region. Average weights of the thyroid at birth as determined by other investigators in other localities show striking differences, as follows: 1.1 Gm. in Firenze, Province, Italy (Castaldi, 1922), 1.53 Gm. at Rome (Eggenberger), 1.9 Gm. at Kiel, Germany (Wegelin), 2.5 Gm. at Paris (Guiart, cited by Wegelin, 1926), 5.7 Gm. at Berlin (Klöppel), 8.2 Gm. at Bern (Wegelin). The weight of the gland at time of birth is greatest in goitrous regions, generally, the weight is greater in Europe than in America and shows wider variations.

Weight in Adults As the child grows older, the weight of the thyroid, of course, increases, to reach its maximum (normally) in early adult life. Von Kolnitz and Remington (1933) found the average weight of the normal thyroid gland between the ages of 16 and 20 years to be 13.0 Gm. at Charleston, S. C. (non goitrous region), whereas Hellwig recorded 23.2 Gm. as the average weight for normal glands in adolescents of the same age group at Wichita, Kansas (also in a non goitrous region). Normal glands in the same age group were found to have an average weight of 21.6 Gm. at Chicago (Jaffé) and 26.7 Gm. at Minneapolis (Rice).

According to Marine (1932), the normal thyroid weighs between 20 and 25 Gm. and does not exceed 0.35 Gm. per kilogram of body weight, being relatively larger in infants and in women. Boyd (1935) observed that the gland is approximately one third heavier in women than in men, the average weight at the seacoast being between 20 and 30 Gm. and in hilly districts, between 35 and 50 Gm. Jaffé noted an average weight of 27.4 Gm. for the normal gland in white men (Chicago), the average in white women being 28.1 Gm. The normal gland weight, as determined by Von Kolnitz and Remington, in Charleston, S. C., was 20.0 Gm., the weight of the gland in the adult in Minneapolis was found to be approximately 28.0 Gm. (Rice). According to Nolan, in Minnesota, the average weight of the normal thyroid in adult males between 20 and 80 years of age ranges between 22 and 28 Gm. Rice states that the range of normal variability in the weight of the adult gland is from 10 to 50 Gm., a gland weighing 40 or 50 Gm. is not necessarily goitrous, being within the range of normal variability.

Hellwig (1933) noted that the average weight of the normal North American thyroid gland is less than that of the European gland and further that variability in weight is less in the North American gland

Toward the end of the life span the thyroid gland decreases gradually in size and weight provided of course that pathological changes do not take place

RELATIONS WITH CERVICAL FASCIA AND MUSCLES

The thyroid is invested with an internal and an external capsule. The internal capsule consists of fibrous connective tissue that immediately ensheathes the gland and is intimately connected with the fascial coverings of the trachea and larynx. The external capsule is formed by the middle cervical fascia and is continuous laterally with the carotid sheath and the pericardium. On each side a ligamentous band attaches the posteromedial part of each lobe to the cricoid cartilage. The convex lateral surface of the gland is closely covered outside the sheath of pretracheal fascia by the sternothyroid muscle.

The insertion of the sternothyroid into the oblique line of the lamina of the thyroid cartilage renders impossible the upward movement or enlargement of the gland. A space between the postero-lateral border of the sternothyroid and the longus capitis is occupied by the upward extension of the lateral lobe on each side. Above the medial surface of the thyroid lobe makes contact with the inferior constrictor and the posterior portion of the cricothyroid muscles that lie between the thyroid and the side of the cricoid cartilage as well as the posterior part of the thyroid cartilage. The sternocleidomastoid overlies the sternohypoid, sternothyroid and omohyoid, laterally crosses the poles of the gland and usually all but covers the lateral lobe. The superficial fascia forms a thin lamina investing the platysma and with the skin overlies these muscles.

The isthmus anteriorly is covered by the pretracheal fascia which separates it from the sternothyroid muscles over which lie the sternohypoid muscles and the anterior jugular veins as well as the thin superficial fascia and the skin. In most cases along its upper border runs an anastomotic branch between the two superior thyroid arteries. The inferior thyroid veins leave the gland at its lower border.

During deglutition contraction of the stylohyoid muscle carries the

larynx upward and with it the thyroid gland (because of the intimate attachment of the gland to the larynx) The origin and insertion of the cervical fascia and preglanglular muscles do not prevent the downward growth of the enlarging gland into the mediastinum between the middle cervical and prevertebral fascia

Relation to the Parathyroids Usually the parathyroids are situated between the posterior borders of the lobes of the thyroid gland and its capsule As a rule there are two superior parathyroid bodies and two inferior the former being the more constant in position In most cases the superior parathyroid body on each side is found at the level of the lower border of the cricoid cartilage and behind the line of contact of esophagus and pharynx The inferior on each side may be located at the lower edge of the lateral lobe of the thyroid gland or in other cases a short distance beneath the gland at times it is situated beneath the inferior thyroid artery

In still other cases the inferior parathyroid body may be within the structure of the lobe of the thyroid gland and close to the lower end of the posterior border of the thyroid It may lie within or posterior to the fascial sheath of the thyroid gland either below the inferior thyroid artery and close to the lower pole of the lateral lobe or just above the inferior thyroid artery In about one third of cases there are more than four parathyroid bodies whereas there are fewer than four in less than one per cent of cases Scattered islands of parathyroid tissue are of frequent occurrence within the connective tissue and fat of the neck and in the immediate vicinity of the parathyroids proper

The blood supply of the parathyroid bodies is derived from a branch of the inferior thyroid artery or from anastomosing vessels connecting the superior and inferior thyroid arteries The lymphatic systems of the thyroid and parathyroids are intimately related Nerves to the parathyroids may arise from a plexus within the fascia on the posterior portion of the lateral lobe of the thyroid or from the superior or middle cervical ganglia

BLOOD SUPPLY

The blood supply of the thyroid gland is extraordinarily rich The volume of blood per minute per 100 Gm of organ was found by Burton Optiz to be 560 cc for the thyroid which thus receives two to ten times the volume of blood received by other organs of the

body. The blood to the thyroid is supplied mainly by the superior and inferior thyroid arteries. These divide into the parenchymal arteries, which in turn branch into interlobular arteries. The interlobular arteries divide into intralobular arterioles that distribute their blood to the fine network of periacinar capillaries.

The superior thyroid arteries are the first branches of the external carotid from which they originate on the anterior surface to run forward and downward along the *thyrohyoid* and *longus capitis* muscle and between these and the fascia overlying the inferior constrictor of the pharynx, to the superior pole of the gland. The superior belly of the omohyoid muscle is superficial to these vessels.

Divisions of the Superior Thyroid Artery. The superior thyroid divides into the infrahyoid artery (to the regional muscles), the sternomastoid, the superior laryngeal (to the mucosa and intrinsic muscles of the larynx), the cricothyroid artery, and the glandular arteries, usually three in number, as follows: (1) a large lateral and anterior branch coursing down over the anterior surface of the gland to the isthmus, (2) a smaller posterior branch which runs along the posterolateral surface, and (3) a small branch which frequently originates between the anterior and posterior branches and immediately dips into the gland.

Stewart (1932) observed that, in practically all instances, the superior thyroid artery sends its largest branch downward, anteriorly and medially along the border of the lateral lobe to the isthmus, there to anastomose with its fellow of the opposite side. Turning downward, this large branch of the superior thyroid artery frequently runs to the medial portion of the inferior pole. Mastin (1923) found that, in every case examined, the superior thyroid artery and the homolateral inferior thyroid artery communicate directly, a *ramus communicans* arises from the (smaller) posterior branch of the superior thyroid and joins with the inferior thyroid artery of the same side. Also, either from the *ramus communicans* or from the posterior branch of the superior thyroid artery a small vessel takes rise and courses to the superior parathyroid body.

As Rienhoff remarks, ligation of the superior artery at the superior pole of the gland is inadvisable because the vessel may enter the gland anywhere between the apex of the superior pole to the isthmus. Ligation is best performed within the space bounded by the *longus capitis* and

thyrohyoid muscles, a possible higher bifurcation or trifurcation is not to be feared. The vessel may undergo bifurcation or trifurcation two-thirds of the way upward toward its point of origin from the external carotid artery.

We would like to emphasize the fact that the large branches of the thyroid arteries do not dip deeply into the gland but extend over its surface, smaller branches only penetrating into the gland. Profuse peripheral anastomoses of these large branches offer a difficult problem to the surgeon. Mastin found anastomoses between the two superior or one superior and a contralateral inferior artery in 80 per cent of his specimens, in 20 per cent of cases there was direct communication between all vessels. On the lateral and posterior surface of each lobe, the prominent development of the homolateral anastomosis is readily observed, also conspicuous on the surface of the gland are anastomoses between contralateral arteries.

Indirect communicating channels are found as follows. The superior lateral artery communicates with the cricothyroid branch of the superior thyroid artery, to provide an indirect lateral anastomosis. A similar indirect anastomosis forms a channel between the superior and inferior lateral arteries. Union of the inferior laryngeal and the inferior thyroid arteries with the anterior mediastinal branches of the internal mammary arteries and the bronchial arteries give rise to the tracheal plexus of vessels. At times the contralateral inferior laryngeal and the ascending pharyngeal arteries may also intercommunicate about the esophagus.

Variable branches from the superficial trunks extending into the muscles and fascia about the thyroid gland may have numerous indirect channels of communication. It is to be noted that the hyoid, superior laryngeal and cricothyroid branches of the superior thyroid artery may participate in the development of a collateral circulation.

Inferior Thyroid Arteries The inferior thyroid arteries take rise from the thyrocervical trunk, a branch of the subclavian. They run medially to the posterior surface of the lateral lobe near the inferior pole, to course behind and near the carotid sheath and below the common carotid artery. Lying upon the scalenus anticus, the inferior artery on each side emerges from beneath the carotid artery at a point immediately above the level of the tendon of the omohyoid muscle.

The divisions of the inferior artery are (1) a branch to the

scalenus anticus and the inferior constrictor muscles (2) the ascending cervical artery (to the deep neck muscles) and the vertebral arteries (3) the inferior laryngeal artery and (4) the glandular arteries — (a) the small anterior branch which dips into the gland almost immediately and (b) the larger posterior branch that extends almost transversely across the posterior surface of the gland to the posterior medial edge there to ascend so as to form a junction with the superior artery. A small vessel from the posterior branch of the inferior artery runs to the inferior parathyroid body and generally to the superior parathyroid.

In common with other authors we have observed that the inferior thyroid artery is quite variable. Age seems to be a factor the inferior thyroid artery being more prominent in children and elderly persons than the superior artery. According to Mason, the diameter of the inferior thyroid artery is on the average 0.9 mm greater than that of the superior artery.

Following ligation of both the superior and the inferior arteries a collateral circulation may gradually develop through the superior and inferior laryngeal the thyroidea and cricothyroid together with branches of the lingual artery and through the tracheal and esophageal arteries which have connections with the anterior and superior mediastinal and internal mammary arteries.

Thyroidea ima. In some 10 per cent of cases the thyroidea ima appears taking rise usually from the medial surface of the innominate artery but at times from the right common carotid the right or left subclavian or even the internal mammary arteries. As a rule it ascends to the inferior surface of the isthmus and terminates in the isthmus or in the inferior poles of the lateral lobes.

Moss and Horner state that the thyroidea ima is usually smaller than the inferior arteries, one of both of which it may supply.

Arterioles from the Trachea. Arterioles run between the tracheal cartilages and penetrate into the thyroid gland to add to its many sources of blood supply. They serve to emphasize the exceeding richness of the blood supply of the thyroid gland.

PERIACINAR CAPILLARY NETWORK

The intralobular arterioles subdivide into fine capillaries that form a perifollicular meshwork enveloping each follicle. These capillaries are imbedded in the connective tissue around the follicle and, according to certain histologists at least, may be in intimate contact with the epithelial cells. Some observers believe that such an intimate contact facilitates basal secretion of thyroid hormone directly into the blood stream. As Rienhoff remarks, the periacinar network of capillaries is remindful of the glomerular circulation of the kidneys.

VEINS OF THE THYROID GLAND

The perifollicular circulation leads into the efferent vascular system, which is characterized by numerous anastomoses in the immediate neighborhood of the follicle. (In contrast, anastomoses between arteries or between arteries *within the gland* are rarely encountered.) Venules unite to form veins that accompany the arteries to the surface of the gland and there form a large and intricate network situated for the most part between the external and internal capsules. These large and numerous intercommunicating veins are usually double and start in superficial bar anastomoses (Mastin). A superior vein accompanies the superior artery and passes over the common carotid artery to empty into either the internal jugular vein or the lingual vein. One superior vein may empty into the internal jugular vein above the level of the origin of the superior artery from the external carotid and a second superior thyroid vein may empty into the internal jugular vein below this point. Present also in about 90 per cent of cases is a middle or lateral thyroid vein arising from the lateral surface of the gland, this vein, after being joined by the laryngeal and tracheal veins, empties into the lower part of the internal jugular vein.

Communicating freely with the superior and middle thyroid veins after arising from the venous plexus on the surface of the gland, the inferior thyroid veins (usually from two to four in number) take different courses. The left inferior vein frequently runs in front of the trachea and behind the sternomastoid muscle, to empty into the left innominate vein, transverse communicating vessels connect it with its fellow. The right inferior vein may take a similar course, to empty into

the right innominate vein. Occasionally, however, these veins may empty into the subclavian or the internal jugular vein.

Esophageal, tracheal and inferior laryngeal veins are tributary to the larger veins from the thyroid. More often present than the thyroidea ima artery, the vena thyroidea ima arises in most cases from the inferior surface of the isthmus to run down over the surface of the trachea and empties commonly in the left innominate vein. Valves are present at the terminations of the larger veins from the thyroid.

LYMPHATICS OF THE THYROID

Like the arterial and venous systems of the thyroid, the lymphatic system of the gland is manifold and complex. Covering the surface of the gland there is an intricate plexus of anastomosing lymphatic vessels. From them there extend into the gland lesser lymphatics which, for the most part, follow the blood vessels and extend through the interlobular and intralobular connective tissue septa. Arteries, arterioles, veins and venules are encircled by an almost syncytial meshwork of lymphatics which travel on with them to the acini. Broadening of the lymphatic channels has been repeatedly noted. Between the follicles, hence we are led to believe that secretion from the epithelial cells of the follicles into lymph vessels must be taken into account to a greater extent than has been noted by most authors. Certainly, the lymph channels provide passageways for metaplastic growths and toxic principles, surely they must participate in the normal functioning of the gland and the release of the active principle of the thyroid — again normally — to the tissues of the body generally. A number of observers have remarked on the presence of colloid within the lymphatic vessels but have failed to stress the significance of this finding.

Medial lymphatics of the superior area originate from lesser vessels within the upper portion of the isthmus and the medial portion of the superior poles, ascend to the prelaryngeal and thyrothyroid glandules, and finally reach the deep cervical or internal jugular chain between the lymph glands. Lateral lymphatics of the superior area arise from the anterolateral and posterolateral surface of the superior poles of the gland, pass upward laterally in front of and behind the carotid artery, and terminate in the deep cervical glands.

From the inferior portions of the gland, lateral lymphatic vessels arise so as to drain the surfaces of the inferior pole and empty in the

vessels extending to the paratracheal and deep cervical glands. Also, from the medial surface of the inferior poles and the inferior surface of the isthmus, medial lymphatics run to the deep cervical and superior mediastinal glands, as well as drainage to the paratracheal and pretracheal glands.

Definitely direct connections between the lymphatic vessels and the veins have been found by several investigators, no intervening lymph nodes being present in these instances. These direct channels between lymphatic vessels and veins have been described not only in many animals but in man as well.

NERVE SUPPLY

From the superior and middle cervical sympathetic ganglia arise perivascular plexuses of non medullated nerve fibers that accompany the superior and inferior thyroid arteries and are given off to the interfollicular connective tissue in such a way as to form (perifollicular) plexuses encircling the follicles. Neurofibrillae extend from these perifollicular plexuses to the base of each epithelial cell where each filament terminates in a minute bulbous process. In addition, some filaments from the superior and inferior laryngeal nerves pass into the gland.

As Simon (1943) has observed a detailed knowledge of the surgical anatomy of the recurrent laryngeal nerve is indispensable to safe thyroid surgery, anatomists and surgeons, however, give different descriptions of the course and structure of this nerve. According to some authors the nerve lies directly in the tracheoesophageal groove whereas other descriptions state that the nerve lies in a lateral position. Higgins (1927), following a series of dissections, noted that the recurrent laryngeal nerve runs obliquely upward to the side of the trachea from its point of origin. Fowler and Hanson (1929) reported on 200 dissections, according to their determinations, in 65.5 per cent of cases, the nerve was posterior to the inferior thyroid artery and, in 26 per cent of cases, anterior to this artery. The nerve was found to be anterior to the artery on the right side in 18 cases but posterior to the artery on the left in 19 cases out of 22 dissections made by Berlin and Lahey (1929). Carrying out 12 dissections, Ziegelman (1933) reported the following determinations: 17 cases in which the nerve was anterior to the artery, 12 cases in which it was posterior

to the artery, and 13 cases in which the nerve was between the artery and the gland. The findings of Weeks and Hinton (1912) were essentially a confirmation of Ziegelman's determinations, further, they observed that 78 per cent of the nerves divide extralaryngeally, many starting their division at the level of the lower pole of the gland.

Weeks and Hinton stress the fact that the external branch of the superior laryngeal nerve, which accompanies the superior artery, supplies the cricothyroid muscle, a tensor muscle of the larynx, paralysis of this muscle results in hoarseness or a voice that becomes tired after moderate talking.

HISTOLOGY AND CYTOLOGY

Connective tissue septa arising from the internal capsule extend as a network throughout the gland and divide it into *lobules* which are in turn subdivided by thinner septa *primary lobules*. This lobulation is readily observed grossly and microscopically in sections. Further, finer extensions of connective tissue within each primary lobule enclose and separate the histological units of the thyroid gland—the vesicle, or follicles which correspond to the acini of typical alveolar glands and which contain the colloid.

The perfollicular septa are collagenous in nature. A net of fine reticular fibrils lies just inside the collagenous network and is in intimate contact with the follicular epithelium, separating it, according to some authors, from the perfollicular capillaries. Some histological studies, however, indicate that at least some of the numerous capillaries make direct contact with the epithelial cells lining the follicle.

Connective tissue (collagenous and elastic) is distributed not only as fibrous septa along the course of the blood vessels throughout the organ but also in variable amounts as *interfollicular connective tissue* mostly arranged along the larger blood vessels. Nerves and lymphatic vessels as well as arteries and veins thread through the delicate connective tissue framework of the gland.

In infancy, there are especially prominent bands or heavy columns of fibrous tissue which divide the gland into fields. The interlobular stroma at this age thus appears to set off groups of acini that are completely separate from one another. With increasing age of the individual, the broad bands of interlobular stroma gradually lose their prominence and after puberty they are much less distinct. In ad-

vanced age, fibrous connective tissue is enormously increased and the heavy columns of interlobular stroma become prominent again. Such bands of interlobular stroma should not be interpreted as fibrous tissue proliferation resulting from pathologic processes, as in inflammation, when, as a result of inflammation, fibrous tissue invades the lobules, the acini are generally destroyed in large numbers.

THE ACINI

The acini, or follicles, are closed vesicles, irregularly rounded and highly variable in size. They may be spherical, ovoid or even bifurcated. The more centrally located acini are generally larger than those toward the periphery of the lobule and are, presumably, older. In diameter they range from about 0.035 to 1 millimeter. The typical follicle is lined with a single layer of epithelium which surrounds a lumen storing the colloid produced by the lining cells, very early in their development, acini consist only of some three or four cells and do not have a lumen.

In infancy, the acini are small and contain little if any colloid. They reach their maximum size early in adult life. In the later years of life, the size of the acini decreases progressively into old age (Rice, Hertzler). The acini of the senile person at times resemble those typical of the infantile gland, although variation in follicle size within the same senile gland is greater than within the individual gland. During the life span the size of the thyroid gland and the size of the acini increase and decrease in parallel fashion.

In the immature gland, solid masses of epithelial cells give rise to the acini, during early childhood, the proportion of developing acini to fully developed acini is relatively large. After puberty, however, interacinar cell masses — representing undeveloped or developing follicles — are relatively few. There is some evidence (Hertzler, 1939) that the senile follicle shows a tendency to reproduce but is able to give rise only to small and imperfect, perhaps functionless follicles. Such small, abnormal follicles in the senile gland may, however, be merely degenerating follicles (Andrew and Andrew, see page 288).

Follicle size varies considerably from gland to gland, but generally is fairly constant within the same gland. It is affected by numerous factors — state of health, nutrition, medication, age and geographic locality (presumably because of varying availability of iodine). In

goitrous regions the follicles are smallest in non goitrous regions they have the greatest average diameter and in moderately goitrous regions their average size is medium or intermediate between the averages for goitrous and non goitrous regions In Minnesota (moderately goitrous region) Rice determined the average diameter of the follicles in the thyroid gland of the newborn to be approximately 60 microns the average diameters at the ages of 20 years and 60 years being 250 and 200 microns respectively Corresponding figures for the same ages in a non goitrous region (Wichita Kansas) were recorded by Hellwig (1933) as follows 70 microns (newborn) 280 microns (at age of 20 years) and 170 microns (at age 60 years) The acini of the North American gland are on the average larger than those of the thyroid glands of Europeans

THE ACINAR EPITHELIUM

The epithelial cells lining the follicles are highly sensitive to the multiplicity of influences Their size shape structure and activity



Fig 17 Normal acinus (unusually large magnification)

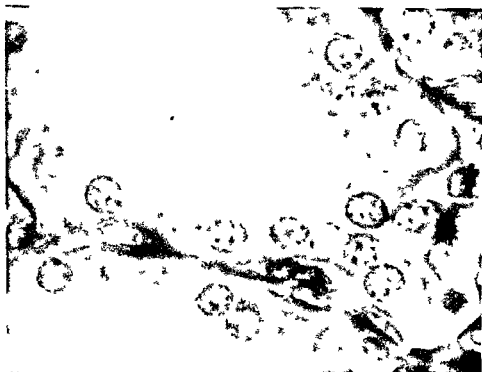


Fig 18 Normal epithelium (unusually large magnification)

(reproductive as well as normal physiological functioning) depend upon the age of the individual geographic locality, nutritional status availability of iodine (past and present) state of health medication temperature (of the gland) hypophyseal activity (thyrotropic hormone) and other factors The height of the cells tends to increase during menstruation and pregnancy

In infancy, these cells are cuboidal As the individual grows older and the acini increases in size some flattening occurs The smaller and more youthful (peripherally located) acini at any age (of the individual) generally possess the higher type of epithelial cell and the smallest amount of colloid During the greater part of adult life, the acinar epithelium most frequently consists of medium cuboidal cells but the apparently normal gland manifests variations ranging from flat or low cuboidal to high cuboidal or from low columnar to flat endotheloid cells Columnar cells however, are rare and restricted to small localized areas, most authorities regard them as definitely a pathological manifestation

The more flat type of cell is usually found in the lining of the

larger, older and more centrally placed follicle, such a follicle contains the largest amount of colloid. The shape of the cell is largely dependent upon the pressure of the colloid. In colloid goiter, the cells are much flattened whereas in exophthalmic goiter, the cells are columnar, hypertrophy and hyperplasia being involved.

The height of the cuboidal cells ranges between 4 and 8 micra. It is believed that cell height and physiological activity run parallel. The higher cells are more active. Two or more nuclei are usually present. The nuclei of such active cells are more vesicular than those of lower, less active cells, and are round or ovoid in shape, their axes being parallel to the cell margins. As a rule, the nuclei occupy positions near the base of the cell. Their network of chromatin is notably fine.

In old age, the epithelial cells become cuboidal as in infancy, this change being associated with the decreased size of the follicle. Low cuboidal cells seem to be characteristic of the senile state, although many flat cells are observed.

Langendorff's colloid cells are now believed to be simply dead or dying epithelial cells quite like those which have been frequently described in many different types of epithelial membranes.

As regards the factor of geographic locality, it seems to be true that proliferation of the follicular epithelium is most extensive in goitrous regions, moderate in moderately goitrous areas, and least extensive in non goitrous regions.

Effects of Thyrotropic Hormone Thyrotropic factor of the anterior pituitary gland causes a rapid activation of the thyroid gland and hypertrophy of the epithelial cells. Reabsorption of colloid and release of thyroid hormone into the circulation are associated effects. Epithelial cell height is markedly increased (Rawson and Starr, 1938), the actual measurement of the height of the thyroid epithelium may be used to determine the degree of hyperplasia produced by thyrotropic substance.

Effects of Thiouracil and Related Substances Administration of thiouracil and related substances cause inhibition of the formation of thyroid hormone and, as a response to consequent excessive production of thyrotropic hormone, there is marked stimulation of growth of the thyroid gland. The acinar cells undergo enlargement (hypertrophy) and multiplication (hyperplasia). The epithelium increases in height and undergoes papillary folding with which is associated loss of

follicular colloid Paschkis et al (1945) have shown that this hyperplasia occurs early in the course of thiouracil administration — within twenty four hours (normal rats) — and increases to a maximum after some ten days to two weeks, afterwards showing a decrease. These workers explain this later diminution in mitotic activity as follows: new formation of cells after the period of maximum activity serves only to maintain the number of cells present. The effects of thiouracil are enhanced by cold.

Effects of Cold Numerous investigations have established that chilling induces an increase in height of the follicular cells. Because thyroid stimulation by exposure to cold is abolished by hypophysectomy or section of the pituitary stalk, this stimulation has been attributed to an increased production of thyrotropic hormone. More recently, however, Turner and Turner (1945) have shown that *in vitro* exposure of thyroid tissue to lowered temperatures (4°C) brings about a marked increase in height of the epithelial cells. These authors suggest the possibility that there is a direct temperature effect upon the cells of the thyroid gland. Increases in cell height are marked within an hour *in vitro* as contrasted with marked increase in cell height after only one half hour exposure to cold in the case of the intact experimental animal. There is evidence that thyroid activity is decreased at higher temperatures (40°C). Turner and Turner point out that the anatomical location of the thyroid in the neck and in intimate contact with the trachea permits the gland to respond rapidly to changes in environmental temperature — an arrangement that may be considered to have physiological significance.

INTRACELLULAR GRANULES AND CELL INCLUSIONS

Mitochondria These bodies, varying in size and shape from very fine granules to straight or curved rods of different lengths, are scattered irregularly throughout the cytoplasm of the epithelial cells. They are found alongside the nucleus as well as at the basal and apical ends, i.e., they exhibit no polarity. As the cell increases in size, the number of mitochondria increases, but their relative number is not an index of the amount of secretion or the toxicity of the gland. Their relation to the metabolism of the cell is still undetermined.

Centrosome A centrosome is situated in the distal portion of the cell near the lumen.

Fat Droplets According to some authors the presence of fat droplets in the distal portion of the cell is evidence in favor of the view that secretion takes place from the basal (proximal) part of the cell

Golgi Net Usually located on the apical side of the nucleus but sometimes on the basal side, a reticular network — the Golgi net — has been assumed by many authors to be an indicator of cell polarity, the assumption being that the network is situated on the secreting side of the nucleus

Secretion Antecedents " Investigators have long sought morphological evidence of secretion antecedents — cytological precursors — of the substance secreted by the cells. Round droplets of colloid were first described by Langendorff. Using special staining methods Bensley (1916) identified a vacuolar substance at the extreme base of the cell (and therefore adjacent to the capillary net). Bensley believed that this substance is discharged directly into the blood stream — according to him the normal direct mode of secretion of the gland. Bensley, however suggested that there is an indirect mode of secretion also, in which the secretion becomes condensed in the cytoplasm in the form of droplets (colloid droplets) having a high content of solids, the colloid droplets are produced when the rate of secretion exceeds the body needs and are extruded into the follicular lumen. As De Robertis has observed (1912), satisfactory cytological data are largely lacking as regards the changes in the intracellular colloid immediately following stimulation of thyroid activity by injection of thyrotropic factor, common histological methods tend to mask the colloid droplets within the cells. De Robertis found that, within a maximum of 60 minutes after injection of thyrotropic factor into rats and guinea pigs, cells are actively secreting toward the lumen, colloid droplets being formed near the nucleus and increasing in size as they move toward the apex of the cell. At points on the apical surface, cytoplasmic bulges containing colloid droplets are released into the lumen by rupture of the pedicle. Hence De Robertis believes that the secretion of the thyroid is apocrine: some of the cytoplasm passing with the colloid (or precursor of the colloid) into the lumen. After this early phase, however, a reversal of the direction of secretion occurs: secretion then being toward the base, at the same time colloid stored within the lumen is reabsorbed. According to De Robertis the chromophobic vacuoles ob-

served by various investigators are fixation artefacts, after preparation of tissue by the freezing drying method, the intrafollicular colloid appears quite homogeneous

More recently, Thomas (1941), in a cytological study of the secretion antecedents of rat thyroids activated by thiourea, observed that Bensley's basal vacuolar substance becomes strikingly apparent and can be seen distinctly in a position usually on the basal side of the nucleus, although at times partly surrounding the nucleus. Generally, the basal vacuolar substance appears as a clear hyaline spherule, in frequently, it may be in the form of globules separated by fine cytoplasmic bridges. Thomas's staining technique gave a very pale blue color to the basal substance whereas colloid droplets nearer the center of the cell took on a dense blue or red color. In the case of large vacuoles shrinkage of their contents may give rise to secondary vacuoles of basal substance at the periphery of the main basal vacuole. Thomas points out that the relation of Bensley's basal substance to intracellular colloid droplets has not yet been established. Further, according to this author, thiourea appears to paralyze the basal secretion of the thyroid by an alteration in the permeability of the cell membrane to the antecedent secretory substance, thus causing its accumulation within the cell. Discharge of intrafollicular colloid however, does not seem to be affected by thiourea and appears to proceed by the normal process of transcellular release of colloid.

Uhlenhuth has repeatedly observed minute granules, stainable in the living cell by use of neutral red, these granules may or may not have significance in relation to secretion. By some, the finding of such inclusions in the proximal portion of the cell is considered evidence in favor of the theory that secretion is toward this side.

INTRAFOLLICULAR COLLOID

The colloid stored within the lumen of the follicle is clear and viscid in the fresh state. After fixation, the colloid in the normal thyroid of the young adult stains deeply with the acid dyes (eosin). Vacuoles frequently observed in the colloid (young adults) may be only fixation artefacts, according to De Robertis and others using the Altmann-Gersh freezing drying technique, vacuoles seem to be rare in normal follicles of living animals. Gersh and Caspersson analyzed colloid by means of the absorption of ultra violet light and found no

evidence to suggest unhomogeneity of the colloid in areas within the same follicle, the chemical nature of colloid may however, vary from follicle to follicle in the same or in different thyroids. From time to time a few desquamated cells may be found within the colloid.

Kingsbury and also Norris (1916) reported that colloid first appears in the human thyroid at about the second or third month of fetal life but Lelkes (1935) found no iodine within the human thyroid until the fourth month of fetal life. Hertzler (1939) has observed that a relatively thin colloid is characteristic of the immature gland (and of patients with exophthalmic goiter). In the young adult the colloid of the normal thyroid is stained deeply and homogeneously with eosin. Leblond (1943), studying the localization of newly administered iodine in the thyroid gland as indicated by radio-iodine, recorded that iodine is rapidly deposited in the colloid there being a greater deposition of iodine in the denser eosinophilic colloid. The iodine is fixed in a form which is insoluble in the fluids used in routine histological techniques. Basophilic colloid accumulates smaller quantities of iodine than does the acidophilic colloid. According to Hamilton (1942), who also used radio-active iodine, the difference between the concentrations of tagged iodine in the epithelial cells and in the colloid is slight. Other investigators have noted that the viscosity of the colloid is reduced after administration of potassium iodide and after injection of thyrotropic hypophyseal hormone. Williams (1944), in his studies on the properties of living thyroid cells and follicles experimentally induced hemorrhage into individual follicles and thus obtained evidence that capillary pressure is greater than colloid pressure and that colloid is not sufficiently different from blood serum to bring about any observable changes in erythrocytes. In another recent report De Robertis stated that intrafollicular colloid diminishes after inversion of cell polarity i.e. when secretion is from the basal end of the cell instead of into the lumen (as immediately following injection of thyrotropic factor).

Hertzler (1939) has made painstaking studies of changes in the colloid as age increases. Whereas in the young adult the colloid stains a homogeneous deep pink with eosin the onset of senility is marked by a gradual change in the colloid from acidophilic to basophilic, colloid of the senile gland refuses eosin and accepts hematoxylin from the usual laboratory stain. Andrew and Andrew (1942) found a

striking lack of homogeneity in the colloid in old age, the amount of colloid being at the same time diminished. These workers noted that in the senile gland the colloid is minutely vacuolated as well as thinner nearer the periphery of the lumen, more solid colloid lying in the center of the follicle. Andrew and Andrew stress the evidence that such vacuolization in old age is not artefactual, some follicles lack colloid entirely whereas in other (senile) follicles the colloid is definitely stratified, with solid, fissured colloid in the center and thinner, finely vacuolated colloid next to the epithelial cells.

INTERFOLLICULAR CELLS

A small number of lymphocytes and macrophages are normally present in the interfollicular connective tissue. Diffuse or nodular lymphatic tissue, when encountered in the stroma of the thyroid gland is of pathological significance (see page 204). Occasionally, in other wise normal thyroid glands, portions of displaced parathyroid tissue may be observed, less frequently, bits of thymic tissue may be present.

Interfollicular Epithelial Cells. Small and large groups of interfollicular epithelial cells, no distinct lumen being observable, have often been described. In a certain (probably small) percentage of cases, such cell groups may be fetal rests. In many instances, however, tangential sections through only a portion of a follicle, i.e., through a dome of an underlying acinus, may produce the misleading picture of interfollicular masses of epithelial cells. Then the cut is through just the apex of the follicle and not through the lumen, which another and deeper section would show.

A number of observers have reported histological evidence indicating that new follicles may be formed by budding, but, if budding actually occurs, it must be frequent. New follicles are seldom formed after puberty. In old age, however, according to Rice (1938), not only is there a marked increase in interacinar connective tissue but also many interacinar groups of epithelial cells are characteristically present. So-called buds in the normal gland of the young adult are probably in most cases artefactual, an irregularly twisted follicle having entered the plane of the section.

Hertzler states that in childhood, clumps of epithelial cells are present between well formed acini, the interacinar aggregations possessing no lumen (and, of course, no colloid). He points out that a well

defined transformation is to be observed as follicles develop (1) clumps of cells without a lumen, (2) developing acini with a small lumen and a small quantity of colloid, and (3) mature acini, each with lumen and normal amount of colloid. The older the child the smaller is the number of such cell clumps (partially developed acini), after puberty, only a few such clumps are to be found. In the aged, Hertzler notes, the acini exhibit a tendency to reproduce themselves but succeed merely in producing small acini with flat cells or cell clumps without lumen or colloid. Whether or not such irregularly formed acini function has not been determined.

Andrew and Andrew (1912) offer considerable evidence to support the view that, in old age, such interacinar collections of epithelial cells represent degenerate acini, robbed of their stored secretion and no longer capable of secretion, having been forced into mere clumps of cells by the encroachment of connective tissue.

Thomas (1914) reports having been able to observe the formation of true para-follicular cell nests following stimulation of the thyroid glands of rats by administration of thiourea. These cell nests appear to be derived from the follicular epithelial lining. Other investigators have reported the observation of migration of argyrophil para-follicular cells from the follicles into the surrounding connective tissue (rabbits and dogs).

NODULES IN AN OTHERWISE NORMAL GLAND

We may define a nodule as a localized area of new growth taking its rise within a lobule. It is believed that metaplasia of the epithelial cells within a circumscribed area results in the formation of a nodule which thus represents a secondary lobule made up of normal thyroid tissue that has been displaced. Such nodules are frequently found in glands which appear to be quite normal otherwise. Compression and some consequent alteration of the thyroid tissue in the immediate vicinity of the nodule are observed, but pathological changes in the other portions of the gland have not been shown to result from the presence of the nodules.

Nodules are extremely rare in infancy. At puberty, some two to three per cent of otherwise normal thyroid glands will be found upon histological examination to have nodules. The incidence increases markedly with age. Rice (1938) states that in Minnesota the incidence

may be expressed by the same figure as the age of the group of individuals under consideration, thus, approximately 30 per cent of a group of individuals thirty years old have nodules within their thyroid glands. In advanced life, nodules are present in most thyroids. Nodules are not by any means always palpable clinically but are observed in gross serial sections.

According to a number of authors, nodules probably originate as a result of physiologic response to stimulation during life, especially during periods of physiological stress such as puberty in both males and females and the child bearing period in women.

Their incidence is higher in women than in men and is higher in goitrous than in non goitrous regions. Clerc (1912) observed nodules in almost all thyroids of individuals more than fifty years of age in Bern. Jaffe (1930) reported an incidence of 30 per cent in males and 44.7 per cent in females in Chicago. Rice (1931) in Minnesota found nodules in 43.8 per cent of thyroids from males and 53.1 per cent of those from females. At Wichita, Kansas the incidence as determined in males was 36.7 per cent and, in females, 40.0 per cent (Hellwig 1933). As Nolan (1938) has observed, the average weight of the nodular thyroid is considerably greater than that of quite normal thyroids in all age groups of both sexes.

Nodules differ widely in histologic structure. Their follicles are of all sizes and shapes, often the epithelial cells are comparatively small. Interacinar epithelium may be sparse or abundant. Rice (1938) has remarked on the occurrence of bands of fibrous or hyaline stroma but states that no true interlobular stroma is identifiable. He classifies nodules into four groups as follows: (1) Colloid nodules, with large acini which are filled with colloid. (2) Parenchymatous (fetal) nodules with small acini and presenting the appearance of fetal thyroid, i.e., showing solid packs of epithelial cells. (3) Nodules of mixed type, having a histologic structure in which the characteristics of both parenchymatous and colloid nodules are encountered. (4) Degenerate nodules, showing hemorrhage, cystic formation, calcification and hyalinization, such degenerative changes may be found in any of the other types of nodules.

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CHAPTER V

PHYSIOLOGICAL ASPECTS

PHYSIOLOGY OF THE THYROID GLAND

Secretory Activity. The thyroid gland has as its great if not sole function the production and storage of the hormone, thyroglobulin or thyroxin, which has highly important roles in metabolism, growth, and development. The secretory units are the acini, or follicles, their cells elaborate the thyroid colloid and store it within the follicle lumen. Algire, in his studies of the thyroid gland of the living salamander, has found evidence that the thyroid cells may secrete the colloid directly into the circulation rather than into the follicle. Other authors state, however, that the colloid normally passes first into the follicle, and thence into the circulation (Williams and De Robertis). Lerman was unable to detect thyroglobulin in the blood of the thyroid vein or in the peripheral blood of either normal persons or persons with thyroid disease. Hence, he suggests that enzymic digestion of the large thyroglobulin molecule must occur in order to permit diffusion of active fragments (especially thyroxin) through the follicle membrane. De Robertis has found proteolytic enzyme activity in colloid extracted from single follicles of rat thyroid, presumably, these proteolytic enzymes are the ones which bring about digestion of thyroglobulin so that its fragments may pass through the semipermeable follicle wall. Obviously these considerations raise the problem of the chemical nature of thyroid hormone.

Chemical Nature of Thyroid Hormone. As early as 1874, Gull reported a cretinoid syndrome supervening in adult life in women, this condition being associated with spontaneous atrophy of the thyroid. Later, Reverdin and Kocher (in 1883) noted that a closely similar syndrome ensued from total removal of the thyroid. As a result, the existence of an active principle manufactured by the thyroid was soon surmised. And by 1891 Murray was subcutaneously injecting a preparation of sheep thyroid to treat hyperthyroidism in human beings. Within a year, MacKenzie and Iox had observed that oral administra-

tion of thyroid preparation is as effective orally, in suitable dosage, as when injected. Magnus Levy next discovered (1895) the effect of thyroid on metabolic rate. As soon as the existence of an active constituent thyroid was universally recognized, efforts to isolate it were instituted. In 1896, Baumann discovered that the thyroid contains iodine in organic combination. This iodine is bound to a globulin to form iodothyroglobulin, which is as active physiologically in hypothyroidism as is whole thyroid (Hutchinson and Oswald). Baumann, Oswald, and other investigators obtained highly potent protein fractions, which were also high in iodine content, from the colloid of thyroid. It was not until 1915, however, that E. C. Kendall announced the isolation, in crystalline form, of a compound thyroxin — containing iodine and having the physiological activity of the long sought thyroid principle. Kendall obtained thyroxin from among the hydrolytic products of thyroglobulin. This substance was later (1926) shown to be an amino acid (Harington).

In 1927, Harington and Barger combined two molecules of the amino acid, diiodotyrosine, to synthesize thyroxin. With Randall, Harington isolated diiodotyrosine from thyroid in 1929, it has been shown that thyroxin is 10,000 times more active pharmacologically than diiodotyrosine. Further, thyroxin accounts for only 30 per cent of the total iodine of normal whole thyroid whereas the remaining 70 per cent is combined as diiodotyrosine. No other iodine-containing compounds have been isolated from thyroid materials.

Thyroxin can be made outside the thyroid gland. The administration of inorganic iodine to completely thyroidectomized animals will raise the basal metabolic rate and will produce the specific changes in the epiphyses of the long bones characteristic of the action of thyroxin. The thyroid, however, in all probability is not simply a collection depot for the hormone which is formed in tissues other than those of the thyroid. Administered inorganic iodine is stored in the normal thyroid at eight times the rate at which it would be expected to pass into the gland if a uniform distribution throughout the body were to be assumed. Iodine is accumulated by the hyperplastic thyroid 300-400 times as rapidly as by other tissues. It must be assumed that although other tissues can manufacture thyroxin, the thyroid is an organ specialized for the production of the hormone at a far higher rate than is possible for any other tissue.

Other studies indicate that most of the blood iodine is in organic form, bound to protein and can be separated into 'thyroxin like' and 'diiodotyrosine like' fractions, the ratio of these fractions being the same as that of thyroxin to diiodotyrosine in thyroglobulin. But the blood does contain circulating hormone, there being a higher hormone level in hyperthyroidism than in hypothyroid patients or normal individuals. The present evidence indicates that thyroxin is not the circulating hormone, *in vitro* thyroglobulin increases the metabolic rate of tissues, whereas thyroxin does not. The thyroxin like fraction does not appear to be thyroxin.

In 1930, Harington and Salter reported the isolation of a polypeptide containing thyroxin, 50 per cent of this substance is iodine. Thyroxin polypeptide has been shown to have the same physiologic activity (in terms of calorogenic action) orally or intravenously. On the basis of iodine content, thyroxin and thyroxin polypeptide have the same physiologic potency, but, paradoxically, the potency of whole thyroid is markedly greater than that of thyroxin polypeptide containing an identical percentage of thyroxin iodine. Apparently, the calorogenic activity of whole thyroid depends upon total organic iodine, rather than upon thyroxin iodine. Harington and Salter have suggested an explanation of the fact that whole thyroid iodine is more active than the total thyroxin present—a peculiar peptide linkage within whole thyroid and, possibly, a peculiar optical activity resulting from the peptide linkage. Salter and Lerman have synthesized an active protein from a practically inert diiodotyrosine, this may be regarded as evidence supporting the explanation of Harington and Salter. Discussing the biochemical basis of thyroid function, Harington has expressed his belief that the thyroglobulin molecule has higher physiologic activity because of the existence of a special linkage between thyroxin and diiodotyrosine, this linkage is split when thyroglobulin is hydrolyzed to obtain thyroxin. It is obvious that the true active principle of the gland remains unrevealed.

Calorogenic Action The primary action of thyroid hormone is its calorogenic action—that is, the effect of the hormone on the metabolic rate and heat production. Under the influence of the hormone, the cells metabolize at a faster rate, as a result, oxygen consumption and carbon dioxide production are accelerated, while urinary nitrogen increases. Some sixty to eighty days subsequent to extirpation of thyroid

tissue, metabolism declines to approximately 40-45 per cent below normal. If thyroid is then administered, the metabolic rate is increased, the extent of the increase in metabolic rate depends upon the dosage. The cells of all tissues seem to be affected, but, despite the increased rate of metabolism, the relative rates of oxidation of carbohydrate, fat and protein remain unchanged and the respiratory quotient is not altered. *In vitro* tissue from thyroidectomized animals has a low metabolic rate, whereas tissue from hyperthyroid animals has a high metabolic rate. Also, *in vitro*, thyroglobulin causes an increase in the metabolism of tissues. Thus, the calorogenic action of the hormone does not depend upon muscular or nervous activity or upon the functioning of the adrenal glands. It is generally believed that the thyroid hormone is not itself an independent, direct acting catalyst but that it exerts its action through its effects on the respiratory enzymes within all tissues. Zondek, however, has suggested that the hormone does exert its effect directly on the cell, but is not enzyme like, its effect depends upon the presence of intact, living cells. Other reports indicate that thyroid hormone may increase the activity and even the quantity of respiratory enzymes. It is evident that the precise way in which thyroid hormone increases the rate of oxidative reactions is still undetermined.

Actions on Growth and Development The presence of adequate thyroid hormone is indispensable to normal growth and development. Cretinism, with its dwarfism and juvenile habitus, is a result of congenital athyreosis. In juvenile myxedema, epiphyseal union and the development of ossification centers are delayed. Sexual development is retarded and ultimately stunted. Experiments on young, developing animals likewise demonstrate the importance of thyroid hormone in controlling growth and maturation. Thyroidectomy is followed by retarded physical, sexual, and mental development and by permanent stunting. Administration of thyroid accelerates metamorphosis and rate of maturing of amphibia. In mammals, accelerated growth of epiphyseal cartilage results from thyroid administration, eruption of teeth occurs earlier than normal. If instituted early enough in juvenile myxedema, thyroid therapy can make efficient use of the maturation stimulating properties of the hormone to induce resumption of growth and development. Nevertheless, in many cases, hypothyroidism and its effects are never satisfactorily counteracted, the patient being subnormal physically and mentally throughout his life. In adult myxedema, the



A

B

Fig 19A and B Sporadic cretinism In Fig 19A the appearance of the boy age five before treatment is shown Note the supraclavicular pads of fat the scanty hair and the coarse features In Fig 19B the improvement following treatment is illustrated Note the disappearance of the supraclavicular pads the growth of hair and the improvement in the features (From Joll C A *Diseases of the Thyroid Gland* London Wm Heinemann Medical Books Ltd)

epidermal cells do not reproduce at normal rates and the growth of nails and hair is retarded In growth and development the role of thyroid hormone is fundamentally different from that of pituitary growth hormone normal growth of hypophysectomized animals is not promoted by thyroid hormone Normal growth depends upon the normal functioning of both the thyroid and the pituitary

Relation of Thyroid Hormone to Food Factors High protein diets eventually induce thyroid hyperplasia in experimental animals goitrous enlargement similarly ensues from prolonged feeding of high fat diets cabbage fed to rabbits has been shown to be goiterogenous because of its cyanide content alfalfa hay has a like effect for the same reason Vitamin deficiencies (especially vitamin D deficiency) will likewise result in hypertrophy and hyperplasia of the



A

B

Fig. 20 Skiagraphs of the right foot at the age of five years (A) Sporadic cretinism (B) Normal child. Note that in (A) only four tarsal bones have ossification centers while in (B) seven are to be seen and in addition the epiphyses for the base of the first and for the heads of the other metatarsals are visible. (From Joll C. A. *Diseases of the Thyroid Gland* London Wm Heinemann Medical Books Ltd.)

gland. Inanition may actually suppress the production of thyrotropic hormone and thus cause the thyroid to undergo involution.

On the other hand some workers have reported an antagonism between certain vitamins and thyroid hormone. Vitamin A for instance has been reported to be more rapidly destroyed in hyperthyroidism than in the normal individual. Lewis has found that vitamin C is excreted in diminished amounts following the onset of hyperthyroidism. Various other investigators have claimed that vitamin metabolism

is in one way or another affected by the level of thyroid activity. Nevertheless only two findings seem established definitely with regard to thyroid and the metabolism of the various food factors (1) unbalanced diets have adverse effects on thyroid activity, generally causing thyroid enlargement, and (2) in hyperthyroidism, there is an increased requirement for all nutrients, including the vitamins.

Influence on Carbohydrate Metabolism Probably as a result of the calorogenic action of thyroid hormone, the level of thyroid activity has influences on carbohydrate metabolism. Althausen and Stockholm have observed that the absorption of different sugars is retarded in thyroidectomized animals and accelerated in animals receiving thyroid or thyroxin. Dextrose tolerance tests in myxedematous patients and in cases of exophthalmic goiter would therefore seem to reflect or indicate levels of thyroid activity. Depletion of hepatic glycogen sugar and protein results from administration of thyroid or thyroxin. Sternheimer noted changes in liver glycogen following a single injection of thyroxin the changes occurring before the rise in oxygen consumption. Thyroid administration is known to be a disturbing factor in hypothyroid patients with diabetes mellitus, onset of hyperthyroidism in mild diabetes often causes an exacerbation of the patient's condition. Thyroidectomy is followed, in experimental animals by excessive storage of hepatic glycogen. In certain instances, total thyroidectomy has been used as a therapeutic measure in diabetes mellitus.

Effects on the Nervous System The nervous system like the other systems of the body, reflects the activity of the thyroid gland. As a rule, during hypofunction of the gland, there is a low level of mental and emotional activity, cerebration is retarded, memory lapses occur, and sensory acuity is diminished. The whole nervous system seems sluggish, the vegetative nervous system shows lowered functioning, vasomotor and peristaltic activity being diminished. In hyperthyroidism, irritability of the entire nervous system is increased to such an extent in many cases that nervousness and emotional instability is manifested, headache and tremors being frequent results of the higher intensity of reaction.

The electroencephalogram provides an objective means of measuring physiologic activity of the human brain. In myxedema, the cerebral cortical alpha rhythm is characterized by a comparatively low fre-

quency and low amplitude. As a consequence of thyroid administration, frequency and amplitude of the alpha waves rise to normal. At the same time, the patient's mental response attains a higher level and the vegetative nervous system increases the tempo of its activity.

Effects on the Circulatory System Normal thyroid function is an important factor in normal circulatory action. In hypothyroidism, there is a reduction in cardiac irritability and tone and in the minute volume of the heart, pulse pressure falls and circulation time is prolonged. Myxedematous changes in the heart muscles cause a decrease in cardiac efficiency, the heart being enlarged and flabby. There may be decompensation, with pitting edema of the extremities. The electrocardiogram is altered from the normal, the amplitude of all complexes being less than normal, in leads 1, 2 and 3 the T waves may be inverted. As a rule, these circulatory abnormalities characteristic of myxedema disappear and the functioning of the circulatory system returns to normal following administration of thyroid in adequate dosage.

Hyperthyroidism is featured by increased pulse rate, palpitation, high pulse pressure, and generally a bounding pulse. There is some evidence that a substance having a specific stimulating effect upon the heart rate is elaborated by the thyroid, this substance is presumably distinct from the principle exerting calorogenic action. Lerman has suggested that direct action of the thyroid hormone on the cardiac musculature may explain the lowered cardiac tone in myxedema and the increased tone irritability in thyrotoxicosis.

Hematopoiesis and the Thyroid Myxedema is often accompanied by a secondary anemia. Administration of thyroid usually brings about a gradual restoration of the normal blood picture. A severe anemia of the aplastic type associated with atrophy of the thyroid acini and sclerosis of the gland was reported by Jaffe in 1938. Lerman and Castle have pointed out that pernicious anemia and myxedema may coexist. Many patients with pernicious anemia, however, have an increased metabolic rate.

Effect on Serum Cholesterol Thyroid hormone has been reported by many investigators to have effects on blood cholesterol level. In many cases, hypofunction of the thyroid is accompanied by an increase in serum cholesterol, a decline of serum cholesterol to within the normal range may follow administration of thyroid. Correspondingly,

in hyperthyroidism blood cholesterol is lowered Wilkins and Fleischman have noted variations in the serum cholesterol content following administration of thyroxin, they believe that such variations may aid in the diagnosis of doubtful cases of thyroid dysfunction. Possibly, the lower metabolism in hypothyroidism involves a less complete oxidation so that the cholesterol content of the blood rises, whereas in hyperthyroidism the more intense metabolism causes a more complete combustion of lipid so that the cholesterol level in the tissues and body fluids is lowered. Definite conclusions must be reserved, however, because all workers have not noted marked differences in serum cholesterol levels under varying conditions of thyroid activity or following administration of thyroid or thyroxin.

Thyroid Hormone and Water Metabolism Normal water metabolism involves the activity of the thyroid hormone, which has effects on the distribution of proteins and salts. According to Boothby and co workers, extra protein — deposit protein — is stored in the body fluids in myxedema, rapid oxidation of this deposit protein results from administration of thyroid, and the extra water and salts previously bound to the protein are excreted. It has been suggested that the deposit protein is a mucoprotein possibly derived from the cellular ground substance. Plasma volume is decreased in hypothyroidism and plasma protein is increased, Thompson has found that administration of thyroid brings about a return to normal. To some degree in the normal subject as in the myxedematous patient, thyroid is diuretic. Byron has found that, in hyperthyroidism, the diuresis subsequent to thyroid administration is accompanied by a loss chiefly of sodium salts, whereas chiefly potassium salts are eliminated following the diuresis brought about in normal subjects by dosage with thyroid. Consequently, it is believed that the fluids thus lost in myxedema are derived largely from extracellular sources, whereas, in normal subjects thyroid induced diuresis is largely at the expense of intercellular sources.

Thyroid Hormone and the Metabolism of Inorganic Salts The level of thyroid activity has important effects of the metabolism of inorganic salts. In hypothyroidism, urinary excretion of calcium is decreased, bone density being increased, but in hyperthyroidism, decalcification of the skeleton may take place, urinary calcium being at a higher than normal level. Nevertheless, in both conditions, serum cal

cium levels are normal. Thyroid administration to myxedematous patients brings about higher calcium retention. Phosphorus metabolism is influenced in parallel fashion, the rate of exchange of phosphorus being diminished in hypothyroidism and increased in hyperthyroidism. Studies on the effect of hyperthyroidism upon the chemical composition of bone have demonstrated that thyroid hormone in excess disturbs the normal deposition of calcium and phosphorus and thus may bring about retardation of bone formation.

The important effects of thyroid hormone on metabolism of salts are strikingly shown in the precipitation of an Addisonian crisis by the unwise administration of thyroid to patients with hypothyroidism secondary to pituitary dysfunction. Thyroid hormone causes increased urinary excretion of sodium and chloride. In primary hypothyroidism, urinary excretion of chloride is lower than normal, thyroid administration increases the rate of urinary elimination of chloride usually to the normal rate.

In hypothyroidism secondary to pituitary dysfunction, however, the urinary excretion of sodium and chloride is high because of adrenal cortex insufficiency, the levels in the blood being abnormally low. Thyroid administration in such a case increases the already excessive elimination of sodium and chloride, and thus induces a crisis.

Muscular Response to Thyroid Hormone In hypothyroidism, the muscles generally exhibit hypotonicity, an indication of the interstitial edema of the fibers which is observed upon histological examination. Myxedematous infiltration of the cardiac musculature is common, administration of thyroid reverses the changes and the heart size is restored to normal as the edema disappears. Thyroid hormone increases muscular tone and irritability, as in hyperthyroidism. On the other hand, in hyperthyroidism definite degenerative changes in muscles may occur. Thyrotoxicosis may lead to myasthenia and, in advanced cases, to severe muscular atrophy.

THE THYROID AND THE ENDOCRINE SYSTEM

The thyroid is one of the units in the endocrine system and therefore influences and is influenced by the other glands of this integrated group.

Relation to the Pituitary As is universally recognized, the hormones of the anterior lobe of the hypophysis exert effects upon all the

other endocrine glands including of course, the thyroid. Injections of thyrotropic extract induce the changes characteristic of exophthalmic goiter — *increased size of thyroid, loss of colloid, and iodine, cellular hyperplasia and hypertrophy, and development of the irregular type of follicles.* There is further, a rapid increase in metabolic rate. Massive doses of thyrotropic extract may in certain instances have beneficial effects in hypothyroidism resulting from hypofunction of the pituitary.

Involution of the thyroid is a sequel to pituitarectomy, as many investigations have demonstrated, but in most cases a full blown atyreosis does not ensue the dominant feature being myxedema. Hyperactivity of the thyroid appears to cause a reduction of the output of thyrotropic hormone by the pituitary. Involution of the pituitary follows administration of thyroid, which also increases the gonadotropic potency of the former gland. As early as 1888, Rogowitsch demonstrated that *total thyroidectomy results in pituitary hypertrophy in rabbits.* Atrophy of the thyroid may be produced by thyroxin administration the atrophy is similar to that observed following hypophysectomy and has been attributed to the depressing effect of thyroxin on the anterior lobe of the pituitary.

Relation to the Adrenal Cortex Hypertrophy of the adrenal cortex may be brought about by administration of thyroid. Moreover, doses of thyroid have been known to precipitate a crisis of adrenal failure (Addisonian crisis) in patients with hypofunction of the adrenal cortex the crisis is in all probability the result of increased excretion of salt as in hypothyroidism secondary to pituitary dysfunction. Desoxycorticosterone, as has been shown in experimental animals, not only may counteract the calorogenic action of thyroxin but also may hinder the enlargement of the adrenal cortex that would otherwise result from thyroid administration.

Relation to Adrenal Medulla Thyroid administration increases the sensitivity of response to epinephrine, and in hyperthyroidism the same exaggerated response is characteristic — hence the Goetsch test for hyperthyroidism. Lerman has suggested the possibility that *hypofunction of the adrenal medulla may be a factor in the genesis of hyperthyroidism in human beings.*

Relation to Sterility and Abortion In hyperthyroidism, fertility is reduced, thyroid administration tends to restore normal reproductive function. Even when no definite cause can be determined, both sterility

and habitual abortion may respond favorably to thyroid hormone. Hertoghe has pointed out that, in a great many cases, thyroid is an excellent therapeutic agent in cases of inexplicable sterility. Means believes that, 'with the exception of true myxedema, there are perhaps no conditions in which the use of thyroid is more important than in the treatment of sterility and habitual abortion, thyroid should be prescribed in any case of infertility not traceable to some definite local cause. This applies whether the basal metabolism is standard or substandard. In fact, it has been repeatedly reported that small doses of thyroid promote conception in women who have previously been unable to become pregnant and, also, that moderate thyroid rations tend to prevent abortion in those women who have previously aborted. It has been shown, moreover, that the male gonad is stimulated by thyroid hormone. Spermatogenesis has been improved and fertility increased by the administration of thyroid to patients who had many defective spermatozoa.

Nevertheless, the relationship of thyroid hormone to reproductive capacity remains quite obscure. It is possible that the more intense metabolism induced by supplying the hormone in larger than ordinary quantities may bring about heightened functioning of the reproductive organs and perhaps have a beneficial effect upon the metabolism of spermatozoa and ova.

Relation to Menstrual Disturbances Gratifying results are often obtained when thyroid is administered in cases of menstrual disorders whose etiology may be quite obscure. The physiological influences involved in such amelioration of these dysfunctions of the female reproductive system are not known. Nevertheless, the successes reported are both numerous and impressive. In one series of cases, Mussey and Haines administered desiccated thyroid to 22 patients who had had periods of amenorrhea, 59 per cent menstruated more regularly after receiving thyroid. These workers have reported beneficial effects in a larger number of patients with menorrhagia, oligomenorrhea, and amenorrhea. The basal metabolic rate was low but myxedema was not present. In 73 per cent of the cases of menorrhagia, 72 per cent of the cases of amenorrhea, and 55 per cent of the patients with oligomenorrhea, menstrual flow was definitely rendered more nearly normal. General health was improved in 75 per cent of the patients after elevation of basal metabolism to within the normal range.

IODINE AND THYROID PHYSIOLOGY

The iodine supply and the iodine content of the thyroid are important factors in its normal and abnormal functioning. Iodine intake is the most important factor among those determining the iodine content of the gland, and small differences in this intake are reflected in the total iodine content. When smaller doses of iodine are administered, a relatively higher percentage of iodine is fixed by the thyroid than when larger doses are given. After iodine ingestion, the iodine is taken up by the blood stream, which quickly transports it to the thyroid. The gland rapidly converts the iodine into organic compounds. Within a few hours, these iodine compounds are present in the general circulation.

Iodine is stored in the thyroid in the form of thyroxin and diiodo tyrosine. As a rule, the total iodine content of the thyroid varies directly with its weight, but the relative iodine content is inversely proportional to the gland weight, as Baumann observed in 1896. The average human thyroid weighs approximately 25 Gm. and, as the storehouse of iodine, normally contains about 10 mg. of this element. The concentration of iodine in the gland is therefore about 40 mg. per 100 grams of glandular tissue. When the concentration falls below 10 mg. per 100 grams, hyperplasia follows, goiter may develop.

Iodine deficiency may be 'absolute,' as in iodine poor regions. *Relative* deficiency results when the intake is low and there is an increased need for thyroid secretion, as in puberty, pregnancy, lactation, infection, other conditions increasing strain on the organism, conditions hindering absorption of ingested iodine. Endemic goiter and its sequelae, as Marine states, is primarily a result of iodine deficiency, iodine of course being essential to the production of the thyroid hormone into whose structure the iodine-containing amino acids, thyroxin and diiodotyrosine, are integrated. The iodine content of the thyroid is proportional to the amount of the colloid present in the gland. Hence, in colloid goiter, the concentration in the colloid is below normal range. The average total blood iodine, however, may be within the normal range.

In exophthalmic goiter, administration of iodine may or may not cause a decrease in size, usually, there is simply no further enlargement, although occasionally a marked regression may be brought

about As Curtis and Fertman have stated, it has not been definitely proved that the administration of increased amounts of iodine to patients with goiter will ordinarily induce hyperthyroidism On the other hand, supplemental iodine has been shown to be ordinarily beneficial in the preventive treatment of endemic goiter Kimball found that the use of iodized salt was followed by the development of hyperthyroidism in only 4 per cent of patients with goitrous adenomas, increased thyroid activity was manifested eventually in 56 per cent of patients with goitrous adenomas who received no supplemental iodine (iodized salt) or iodine medication Iodine supplements in the form of iodized salt or as iodine added to drinking water therefore are assumed to be quite safe for the general population

Nevertheless, an excess of iodine is in all probability obtained by those who habitually use the iodized salt available in this country This salt supplies some 200 mg of iodine per kilogram, if 5 gm of iodized salt is ingested daily, the individual gets 1 mg of iodine, or about 5 times the estimated requirement Marine has expressed the belief that iodine requirements would be met satisfactorily and safely by the use of iodized salt containing only 10 mg of iodine per kilogram

The estimated iodine requirement of the normal thyroid is approximately 0.2 mg daily i.e., somewhere between 100 and 200 micrograms nearer the latter figure for the average adult, weight 70 kg (The pregnant and lactating woman requires somewhat more iodine) The amount of iodine estimated as necessary to maintain normal metabolic activity is 2 micrograms per kilogram of body weight daily, the estimated basal requirement is 1 microgram per day Hence, 3 micrograms per kilogram of body weight can be assumed to meet the daily requirements An adequate iodine supply is essential not only to the elimination of endemic goiter but also to a reduction in the incidence of non toxic adenoma and probably toxic adenoma and carcinoma

SUBSTANCES HAVING CALORIGENIC ACTION

Certain other substances have been reported to have calorigenic action similar to that of thyroid hormone, thyroglobulin, thyroxin and diiodotyrosine Some of these calorigenic compounds are closely related to thyroxin but any alteration in the structure of the thyroxin molecule reduces calorigenic potency Tyrosine has been found to have a calorigenic effect approximately one two thousandth that of thyroxin

Lerman has investigated this effect of tyrosine, which he administered to myxedematous patients in doses as large as 15 Gm daily, this dosage containing the equivalent of the tyrosine in 40 Gm of thyroid protein, he detected no metabolic change

Diiodothyronine has been reported to be fifteen times as active as diiodotyrosine, but one seventeenth as active as thyroxin (Canzanelli and Rapport) Lerman and Salter, however, found that crystalline 3, 5 diiodothyronine has an activity only about one thirtieth to one fortieth that of whole thyroid in terms of iodine Lerman concludes

Thus one must consider a molecule containing two atoms of iodine attached to a tyrosine nucleus as the *minimum requirement* for a substance having thyroxin like physiologic properties He believes that the production of thyroid hormone involves two processes (1) the construction of colloidal molecules from simpler polypeptide chains, and (2) the combination of iodinated tyrosine residues to yield iodinated thyronine residues Cohn, Salter, and Ferry have suggested the mechanism of the second process, these investigators demonstrated that the phenolic groups of diiodotyrosine may undergo conjugation to yield an iodized thyronine nucleus Harington has pointed out that, in all probability, tyrosine is converted into diiodotyrosine, which in turn is to form from thyronine and subsequently, thyroxin It would seem possible that thyroid hormone may be formed simply by the introduction of iodine into the tyrosine nucleus—and presumably this reaction may occur in practically any tissue, although thyroid tissue is specially adapted to the production of thyroxin in large amounts

HYPOFUNCTION

Primary Hypothyroidism Primary hypothyroidism results from absence or loss of secreting tissue (1) in atrophy of unknown etiology (cretinism and spontaneous myxedema), (2) in infection, or (3) in subtotal thyroidectomy

Cretinism (Myxedema of Infancy) Cretinism in the United States has been sporadic — i.e., the cretin is a child of apparently normal parents Endemic cretinism occurs in older countries where endemic goiter has been present through many generations of an iodine deficient population In both sporadic and endemic cretinism the characteristic manifestations of hypothyroidism (myxedema) are observed The

classical picture includes subnormal basal metabolic rate, retarded growth and stunted physical and mental development, sluggishness, dullness, delayed bony development, failure to grow in length, delayed or abnormal dentition, and constipation. If the cretin remains untreated, the typical cretinoid facies appear, the skin becomes dry and scaly and the child develops the characteristic pot belly. Other common symptoms and signs are subnormal genital growth, muscular incoordination, deafness, and various types of mental abnormality.

The classical picture, however, is not always seen. The cerebration may be nearly or quite normal, as may skeletal development. The skeleton may attain normal proportions even if treatment is delayed for a year or two after birth. Nevertheless, almost invariably, even slight delay in administration of thyroid causes irreparable damage to the infant brain. For instance, it may be inadvisable to give any treatment in certain cases of advanced cretinism because the patient has a primitive brain and subnormal emotional control, thyroid administration may overstimulate such patients.

Myxedema Classical myxedema, or marked hypothyroidism in childhood, adolescence and adulthood, commonly presents the following symptoms and signs: subnormal basal metabolism, mental and physical sluggishness, slow heart rate, dullness of the sensorium, distended abdomen, constipation, flatulence, loss of libido, sterility, dry and scaly skin (often yellowish), loss of hair, hoarse voice (swollen tongue and larynx), and puffy appearance of eyelids, face, and hands. In addition, frequently the myxedematous individual complains of vague pains, sensitivity to cold and fatigability. In the female, menstrual disorders are almost always manifested.

The increased weight results from deposition of water, the edema of myxedema is in all probability to be attributed to an albuminous deposit similar to egg albumin. The typical myxedematous appearance usually does not develop until the metabolism falls some 20 to 25 per cent below normal. In complete absence of thyroid activity, basal metabolism may be 40 to 50 per cent below normal. In atypical cases, the basal metabolic rate may be within normal limits, the clinical picture of paradoxical hypothyroidism may still less frequently be seen — the symptoms and signs suggesting hyperthyroidism. The chief presenting symptoms may be psychic anxiety, neurosis, depression, dementia or even mania. Subnormal metabolism, however, is usually

suggestive Response to thyroid is the infallible guide to diagnosis in all doubtful cases

When the thyroid ceases completely to function or is removed, and when treatment is withheld, the basal metabolism does not decline to its lowest level until after two or three months And the symptoms and signs characteristic of myxedema usually do not appear for several more weeks or even months The menstrual flow may be scanty or excessive, there may be delayed or irregular menstruation or even amenorrhea

Known etiologic factors are thyroidectomy, thyroid infection, and, rarely, iodine administration (preoperatively or postoperatively), to patients with exophthalmic goiter The condition may occur following the spontaneous disappearance of exophthalmic goiter Most frequently, the cause of myxedema is quite obscure — spontaneous myxedema Mild myxedema may be present from early childhood and gradually become more severe as the decades pass The condition has its highest incidence during the 4th, 5th and 6th decades The disease is 4 times more frequent among women than among men, the etiologic significance of this fact is unknown

Besides reduction in basal metabolism, other physiological changes are observed in typical cases although by no means in all cases *Blood changes* which may be encountered include secondary anemia, usually of a moderate type but sometimes severe, with the anemia an eosinophilia and basophilia may be associated The total amount of circulating plasma may be diminished Further, plasma water concentration is decreased while the protein concentration is increased The serum cholesterol level is frequently found to be above normal In some cases, the chloride level is decreased, but the total base remains as a rule, constant, because of increased bicarbonate The *circulatory changes* frequently seen are (1) prolongation of circulation time, the minute volume of the heart being markedly reduced, (2) myxedematous infiltration of the cardiac musculature, (3) lowered cardiac efficiency, (4) electrocardiographic changes (see page 99), (5) increased heart size The decompensation and pitting edema sometimes observed as a result of cardiac changes are cleared up by administration of thyroid The *protein content of the cerebrospinal fluid* is in many cases markedly elevated Changes in *calcium metabolism* have been noted on page 101 *Blood iodine* may be within the

normal range but may be expected to be below normal, according to Curtis, the acetone insoluble fraction, presumably containing the thyroid hormone, on the average has a value only half normal and its range barely ascends to lower normal

Secondary Hypothyroidism Secondary hypothyroidism results from hypofunction of the anterior lobe of the pituitary or from hypofunction of the adrenal cortex in Addison's disease. The outstanding etiologic factor is lack of normal stimulation of the thyroid, as by the thyrotropic hormone of the hypophysis. The gland may in many cases be in a resting state and exhibit storage of colloid and low or flat cuboidal epithelium. The basal metabolic rate is commonly subnormal and some symptoms may be relieved by an increase in BMR, effected by judicious use of thyroid. Thyroid administration, however, may precipitate an Addisonian crisis. And even when thyroid is not contraindicated, symptoms may persist after prolonged treatment with thyroid.

SIMPLE GOITER

Although mild hypofunction may infrequently be associated with simple goiter, as a rule there is no demonstrable disorder of thyroid function in this condition. The outstanding cause of simple goiter is iodine deficiency. Nevertheless, certain other factors are involved in the etiology of this disorder: constitutional predisposition, hereditary influences, and diet. Sexual factors too are concerned, the disease being more common in women than in men, its incidence increases during puberty and pregnancy. As McClendon has remarked, the one great etiologic factor is lack of iodine in water and food, and the incidence of simple goiter closely parallels the iodine content of the soil and water supplies throughout the world (see Regional Influences).

Inadequate iodine brings about gradual changes in the physiology of the thyroid. First, the gland exhausts the iodine reserve in the colloid. Then a period of hyperplasia leads to enlargement of the gland.

Nodular Non-toxic Goiter (Non-toxic Adenoma) Simple goiter may be followed by nodular non-toxic goiter, or non-toxic adenoma, various types of degenerative changes being observed in simple goiters of long standing. (Nodules, of course, can also arise from fetal rests.) Usually, administration of iodine prevents further enlargement, al

though there is considerable risk of both thyrotoxicosis and eventual carcinoma

HYPERFUNCTION

Toxic Goiter The etiologic factors in toxic goiter have not yet been determined. The thyroid may be abnormal from birth, some observe congenital disorder being involved. Warthin has stated that there may be an inherent predisposition to toxic goiter in individuals who are born with Grave's constitution (thymicolymphatic constitution). Overproduction of the thyrotropic hormone by the hypophysis is another suggested cause, hyperfunction of the thyroid is at times associated with hyperpituitarism (acromegaly). Thompson and his associates have observed that administration of thyrotropic extract to patients with normal or slightly subnormal basal metabolic rates will cause all the symptoms of toxic goiter except exophthalmos. Nevertheless, as Thompson has pointed out in a recent review, there is so far no positive proof that the pituitary is concerned in the clinical disorder of toxic goiter.

Symptoms and Signs The thyroid is in practically all cases firmer than in the normal person and is almost invariably enlarged. Typically the patient's basal metabolic rate is above normal. Weight loss, of course, is also typical. Nervousness, emotional instability, tremor, muscle weakness, fatigability, and increased perspiration are all characteristic of the condition. Cardiac symptoms are tachycardia, usually with palpitation, systolic thrill and bruit. Some 60 to 70 per cent of cases of exophthalmic goiter show exophthalmos. Frequently, there is lid lag and the eyelids are puffy, some patients may exhibit poor convergence. In crisis, the heart rate rises, weight is lost, weakness increases markedly, nausea and vomiting are regarded as definitely unfavorable symptoms. As a rule, in patients with symmetrically enlarged goiters, emotional instability is more marked than in cases with nodular goiters. Typically, in toxic goiter, the blood iodine is elevated and the excretion of iodine in the urine is simultaneously increased.

Response to Iodine Different cases of toxic goiter respond differently to iodine administration, which is usually followed by a decrease in basal metabolism. In rare instances, the administration of inadequate doses of iodine may bring about an increase in the basal

metabolic rate, if adequate iodine is thereafter administered, there is a decrease in basal metabolism

Hyperthyroidism in Pregnancy and Lactation The thyroid produces increased quantities of its hormone during pregnancy and, as a result, the basal metabolic rate rises. Between 70 and 80 per cent of pregnant women show thyroid hyperplasia. Nevertheless, true hyperthyroidism is rare in pregnancy, sterility usually being associated with hyperthyroidism. When the basal metabolic rate rises unduly, abortion is rendered probable. Nevertheless, hyperthyroid patients who are adequately treated are not likely to abort. Abortion does not cure hyperthyroidism and may precipitate a hyperthyroid crisis. Nursing is inadvisable for lactating mothers with hyperthyroidism, such an additional stress may exacerbate the condition of the patient, who already has a high metabolic rate. During pregnancy, the level of blood iodine is raised and iodine excretion is increased. During lactation considerable iodine is lost in the milk.

REGIONAL INFLUENCES

Chatin, a century ago (1852), stressed the high incidence of goiter in regions where water, soils and foods have a low iodine content. His studies were practically ignored, however, until 1896, when Baumann and his pupils established the fact that iodine is of normal occurrence in the thyroid. It is noteworthy that, two millenia ago, the ancients made empiric use of the ash of sponge and seaweed as a remedy for goiter, but, of course, the presence of iodine was not recognized in seaweed until Courtois in 1811 accidentally obtained sodium iodide as a by product of the burning of kelp. Somewhat later, Sir Humphry Davy and Gay Lussac independently isolated the free element. In 1820, Coindet reported that iodine was a remedy for goiter, but his great discovery fell into disrepute because of the toxic effects resulting from the administration of excessive doses of iodine salts. Until the studies of Marine and his associates the prevalent hypothesis was that goiter is caused by specific toxin or virus. Marine's significant studies on the prevention of simple goiter by the administration of minute quantities of iodine were not begun until just at the end of World War I. Their brilliantly successful outcome stimulated similar efforts throughout the world. Attention was focused on regional influences and a whole series of analyses of the iodine content of soils, drinking

water, and foods in relation to the incidence of goiter was instituted. As McClendon has pointed out, the highest incidence of endemic goiter is found among the Alps, Pyrenees and Himalayas, the Thames Valley in England, certain inhabited districts of New Zealand, the region of the Great Lakes, the Mississippi Basin, and the Pacific North west. In general, because of the iodine rich sea foods consumed, districts on or near the coast are comparatively free of endemic goiter, but there are exceptions, as along the coast of New Zealand. Goiter there is widespread, and in some areas the incidence was once 60 per cent. At one time it was speculated that endemic goiter is most common in limestone regions, this belief has been shown to be untrue.

In 1923, McClendon published the first complete goiter map of the United States. The concentration of iodine in water supplies was compared with the incidence of goiter among the draftees in World War I and the correspondence was found to be almost identical. A survey of the incidence of goiter among school children by Olesen (1929) provided a second goiter map, confirming the findings of McClendon concerning regional influences. The highest incidence of goiter in this country is found in the North West block of states, Colorado, Michigan and Wisconsin. The incidence as determined by Olesen ranges between 10 and 27 per 1,000 of general population. The least goitrous parts of the United States are New England, New Jersey, Maryland, and the entire lower block of states from the Atlantic Coast, along the Gulf of Mexico, and through Texas and New Mexico. The incidence in these non goitrous regions is not greater than 1 per 1,000 of general population. In their most inland sections Massachusetts and Connecticut have approximately the minimum of goitrousness that can be termed endemic.

Local geologic conditions, as is now known, determine the varied distribution of iodine in soil and water throughout the world. It has become evident also that the geographic distribution of iodine determines the iodine concentration of the thyroid because the iodine in edible plants and in water determines the iodine intake. Under natural conditions, the iodine intake is supplied chiefly by the food and to a lesser extent by water and salt. In South Carolina, the soil is rich in iodine and the iodine content of the vegetables produced is higher than in the iodine poor Northern and Western states, the incidence of goiter is low in South Carolina and high in the Northern and Western states.

In Texas, where the soil is rich in iodine, the fat free thyroid has been found to contain 6 mg of iodine per gram, the incidence of goiter is very low. In North Dakota, where iodine deficient soil is prevalent, the fat free thyroid may contain only 3.2 mg per gram, the incidence of goiter is high.

Great Lakes Region The region around the Great Lakes was, until recently, one of the most goitrous not only in the United States but in the world. Marine and his associates selected Akron, Ohio, situated near Lake Erie, as the site of his world famous demonstration of the prophylactic value of iodine in small quantities as a public health measure against endemic goiter. The character and results of the Ohio demonstration gave the first great impetus to the institution of similar prophylaxis in every goitrous part of this and other countries. The studies of Marine and his co-workers extended over a period of two and a half years and were made on a large group of school girls. During two weeks each spring and fall, approximately one half the group received a daily dose of 0.2 Gm of sodium iodide, the remainder of the group acted as controls and received no iodide. Of the girls who had no goiter at the beginning of the test, 0.2 per cent of the 2,190 receiving iodine developed enlarged thyroid glands, whereas 21.5 per cent of the 2,305 controls developed enlarged glands. Of those with initial thyroid enlargement, 65.4 per cent of 1,182 who received iodine showed a reduction in the size of the thyroid at the end of a year. Only 13.8 per cent of the 1,048 goitrous controls showed a similar decrease in gland size. In 1922, the Michigan State Medical Society organized an Iodized Salt Committee, and in 1924 this committee, in cooperation with the state board of health introduced iodized salt, common salt iodized to contain 0.2 per cent sodium iodide. Michigan counties were supplied with the iodized salt and its consumption on an almost universal scale was promoted. Within the next decade the incidence of goiter in the counties using iodized salt decreased 75 to 90 per cent. The incidence of goiter operations in seven large hospitals in Southern Michigan declined from 1,452 in 1927 to 591 in 1933. The generalized use of iodized salt during a twelve year period was followed by a 60 per cent decrease in goiter operations in Michigan hospitals reporting a 17 per cent decrease in all operations. Similar successes have been reported from other goitrous states of the Great Lakes region and the Mississippi Basin.

In Michigan as in other localities it was found that the incidence of goiter was inversely proportional to the iodine content of the water supply in a given locality. In districts where goiter is prevalent there is a striking tendency for the earlier enlargement of the thyroid to occur at puberty. In districts where endemic goiter is not prevalent but the iodine supply is low goiter develops in females at the time of puberty

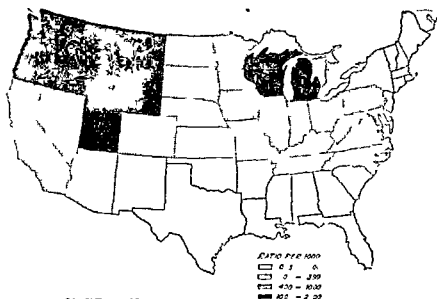


Fig. 21 Distribution of endemic goiter in the United States of America as revealed by thyroid surveys (Olesen 1929)

and during pregnancy. Surveys have shown that the incidence of endemic goiter among school children of both sexes have varied in individual counties in Michigan from 5 per cent or less to as high as 55 per cent. Thyroids from goitrous areas have a lower iodine content, a smaller follicle size, a higher incidence of nodule formation and are larger than normal or even goitrous glands from non goitrous localities.

In Minnesota surveys of school children have shown incidence of endemic goiter as high as 58 per cent. These studies have been correlated with the geographic distribution of iodine in potable waters. For instance, a considerable proportion of the population near Lake Superior derives its water supply from this body of water which contains only 0.01 part of iodine per billion of water. In goitrous sections of

Illinois, the water used for drinking purposes may be obtained, as at Rockford, from deep wells (540-1,500 feet deep), but the iodine content is no higher than that of Lake Superior. The waters of Lake Erie and Lake Ontario have a somewhat higher iodine content, that proportion of the population using these lakes as the source of drinking water has a correspondingly lower incidence of endemic goiter. In Minnesota, the soil also is poor in iodine, and the iodine content of food grown in this state is therefore extremely low. The average iodine content of oats grown in Minnesota has been found to be only 10 mg per metric ton — as compared with an iodine content of 175 mg per metric ton for oats grown in Maine.

Mississippi Basin As regards geographic distribution of iodine, the United States may be roughly divided into two great regions: (1) those areas in which the iodine content of the water is less than 23 parts per billion, and (2) those areas in which the iodine concentration is more than 23 parts per billion of water. The greater portion of the Central Plain of North America — including the Mississippi Basin — lies within the first region, soil as well as water are relatively poor in iodine. It is in this region that the incidence of goiter is highest — areas of low iodine content corresponding quite closely with those in which goiter is most frequently found. Surveys in the Mississippi Basin, however, have shown that in some localities the iodine content of surface waters is low, but goiter is not common. Such exceptions to the general rule occur because a river rich in iodine may flow into a low iodine region or deep wells may extend into the iodine rich salt beds of the Permian region.

Where the iodine supply is moderate, the disease has been found to be confined chiefly to females, some 5 to 8 per cent of males being affected. *Then goiter is most likely to develop during puberty and pregnancy.* In Cincinnati, the ratio of goitrous females to goitrous males is about 1.8 at 14 years of age, 15 years, the ratio is about 2.1. The peak of the incidence for boys is at 13 years, for girls at the age of 16. The most inland parts of Connecticut have a relatively higher natural iodine supply than the Cincinnati area, the latter area is about twice as goitrous as Connecticut. The ratio of goitrous females to goitrous males at age 14 years is 3.7 in Connecticut, at age 15 years it is 5.1. Minnesota, with an endemic goiter incidence approximately three times that of Connecticut, shows a ratio of goitrous females to

goitrous males of only 1.5 at age 14 years, and 2.0 at age 15 years. The geographical influence is also reflected in the loss of iodine by excretion via the kidneys. Curtis and his associates found that in Central Ohio, a moderately goitrous region, the average urinary excretion of iodine by normal adults during a 24 hour period was 51 micrograms, in 5 non goitrous regions, an average of 165 micrograms was excreted daily by normal adults. The average blood iodine of normal individuals in Central Ohio was found to be 4.2 plus or minus 1.2 micrograms per hundred cubic centimeters. Different investigators have differed with respect to the level that is to be recognized as normal blood iodine level, the range is between 3 and 20 micrograms per hundred cubic centimeters. Thus, the determinations in this moderately goitrous region must be considered to represent values near the lowest suggested normal blood iodine level. It must be pointed out, however, that geographic area is only one of the many factors determining blood iodine level, even the method of measuring the iodine content must be taken into account. It is now indubitable that iodine deficiency is the great etiologic factor in endemic goiter. Nevertheless, even in goitrous regions having approximately the same iodine content of soil, food, and potable water there are still inexplicable variations in incidence. And in iodine-rich regions—where the iodine intake by the general population must be considered optimal—there are cases of apparently endemic goiter. Certain individuals would seem to require much larger intakes of iodine than the average. Certain types of diets, especially those which are low in protein, are believed by some investigators to contribute to the development of goiter. The conditions which cause poor utilization must also be considered in future investigations. Finally, there is the problem of goiterogenic food substances that may have adverse effects upon human beings as well as upon experimental animals which have been used to demonstrate the existence of such toxic factors.

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CHAPTER VI—A

IODINE METABOLISM AND BLOOD IODINE

KNOWLEDGE of iodine metabolism under normal and abnormal conditions has been greatly increased in recent years. Many phases of iodine metabolism in various thyroid states have been investigated by studies on blood serum iodine levels as determined by newer techniques of analysis—less cumbersome and more accurate than the older methods. Other investigations of iodine in normal and abnormal physiology have been facilitated by use of radioactive iodine (page 166). The findings have been valuable in confirming or forcing the modification and refinement of theories regarding causal relationships in both hyperthyroidism and hypothyroidism. Of much greater practical significance, however, have been the determinations which are being increasingly applied in the clinic. Thus, more attention is being given to the clinical value of blood iodine analyses. In the diagnosis of hypothyroidism and hyperthyroidism blood iodine determinations are in many cases—although not always—helpful, especially when basal metabolic rate determinations are not enlightening. Changes in the concentration of protein bound iodine in serum have served to indicate the effects of the administration of desiccated thyroid in hypothyroidism and of iodine or thio drug in hyperthyroidism and to give warning of the imminent onset of hypothyroidism in the course of therapy with thiourea, thiouracil or propylthiouracil. Moreover, as we have shown (DeCoursey, 1937, 1938), the level of serum precipitable iodine is indicative of the state of liver function, and blood iodine levels have supplied important evidence of the involvement of the reticuloendothelial system in hyperthyroidism. It seems probable that future advances along these lines will be of prime significance in research laboratory and clinic alike.

IODINE METABOLISM AS AFFECTED BY IODINE THERAPY

Soon after Plummer, in 1922, introduced iodine medication as a *preoperative treatment for exophthalmic goiter*, we adopted this procedure at the DeCourcy Clinic. As first reported in 1933 (DeCourcy, 1933), our observations in thousands of operative cases led us to advance a logical explanation of the action of iodine medication used preoperatively in exophthalmic goiter. In cases preoperatively treated with iodine, we found that at operation the thyroid gland is highly edematous, when the thyroid is cut, a watery fluid drips from its surface. We have not observed this condition of the thyroid gland in cases not treated with Lugol's solution or in simple colloid goiter.

In exophthalmic goiter, as we know, the iodine content of the thyroid gland is depleted. Administration of Lugol's solution leads to rapid formation of colloid material, which causes back pressure on the cells and acini and also on the thin walled vessels surrounding the acini. This back pressure produces the edematous condition found at operation. The improvement in the patient's condition is accounted for as follows. Edema of the thyroid gland depresses the function of the secreting cells, and hence the absorption of possible toxic substances as well as of thyroid hormone into the blood stream is substantially diminished.

How can we explain the fact that improvement is only temporary? In our opinion, after 2 or 3 weeks new blood vessels have been formed and, meanwhile, the older vessels have begun gradually to accommodate themselves to changed conditions. Therefore, even though colloid formation in the gland still continues absorption is resumed and the patient's condition becomes toxic again because the avenues of escape are open. Marine, studying the effects of iodine administration experimentally, reached a similar conclusion.

It is quite possible that we are dealing with 2 secretions from the thyroid gland. Thyroxin produces tachycardia, loss of weight, tremor and increased basal metabolic rate. The other secretion, called the X secretion because of its unknown nature, may activate the thyroxin so as to cause the so-called thyroid crises. Possibly the X secretion combines with iodine so as to form a compound which remains in active so long as iodine is given. The thyroxin secretion is not altered

chemically but only by mechanical obstruction resulting from accumulation of colloid in the acini with consequent back pressure

Assuming that there are 2 thyroid secretions instead of 1, we can explain the difference in surgical attitude toward nodular or adenomatous goiter, on the one hand, and toward hyperplastic goiter on the other. Most of us do not hesitate to operate for a nodular thyroid without previous iodine medication. We do not expect to see a crisis follow. But we would not dare to operate in cases of hyperplastic goiter which have not received preoperative medication with iodine or iodine in conjunction with thiouracil or propylthiouracil.

The temporary improvement following the administration of iodine to patients with Graves' disease has stimulated much research and the findings have been given various interpretations. Plummer (1923), whose work resulted in universal recognition of the value of iodine in the therapy of Graves' disease, proposed a 2 product theory of thyroid secretion in this disorder. He suggested that, in Graves' disease, an incompletely iodinated hormone is secreted and has toxic effects not characteristic of the normal hormone. Iodine therapy, according to Plummer, restores normal, or complete, iodination of the hormone molecule.

Gutman and his co workers (1932) found that, in thyroid glands removed from thyrotoxic patients after iodine therapy, the total and thyroxin like iodine content was as great as in normal human thyroids and sometimes was greater, in contrast were the lower values observed in the thyroid glands of thyrotoxic patients who had received no iodine medication. These observations have been assumed to show that there is an interruption of hormone output as a result of iodine administration to thyrotoxic patients. At least 2 explanations of such an interruption are at once apparent. (1) hormone production may be halted, or (2) if there is no cessation of hormone manufacture, iodine therapy in the thyrotoxicosis may set up some barrier to the release of the hormone into the blood stream.

Loeser and Thompson (1934) proposed the theory that at least part of the action of iodine in thyrotoxicosis is to suppress the secretion of the thyroid stimulating hormone of the pituitary, and Friedgood (1936) suggested that the action of this hormone is prevented by some phase of the action of iodine in thyrotoxic patients. Means and Ler

man (1955), in their study of the action of iodine in thyrotoxicosis, stressed the similarity of the curves of metabolic response to iodine in Graves disease and of the thyroxin delay after thyroidectomy, these workers remarked that the effect of a relatively large supply of iodine must be to block the escape of the thyroid hormone from gland to body.

Salter and Lerman (1936) expressed the belief that in thyrotoxicosis the effect of iodine therapy is the promotion of the synthesis and deposition of the thyroid hormone rather than its release. Salter (1940) concluded that, as a result of such therapy, 'the gland is made to secrete internally into its follicles rather than externally into the blood stream, thus iodine in excess may be said to reverse the direction of the flow of the hormone.

The conclusions of Loeser and Thompson, of Friedgood, of Means and Lerman, and of Salter and Lerman may be viewed as evidence favoring our theory of the action of iodine in thyrotoxicosis. The edematous condition of the thyroid gland as observed at operation must be assumed to retard circulation and therefore to account for the reduction in activity as noted by these several authorities—such a *reduction in activity* being the prime basis upon which they have founded their hypotheses.

Rawson and his collaborators (1945) suggested, in contrast to Plummer's two-product theory, the theory that iodine has two distinct actions in thyrotoxicosis (1) an iodinating action, and (2) an involuting action. As these authors pointed out, a sufficiently large and sustained dosage of thiouracil keeps in abeyance the utilization of iodine for hormone production by the thyroid gland, because of pituitary stimulation, the thyroid gland becomes hyperplastic during prolonged administration of thiouracil, which continues to prevent iodination of the thyroid hormone. Iodine was administered along with thiouracil to patients with Graves disease, and it was found that while the goitrogenic drug continues, under these conditions, to suppress the iodinating action, the iodine medication induces involution of the thyroid gland. Thus, according to Rawson and his associates, it is possible to separate the iodinating action from the involuting action of iodine therapy in thyrotoxicosis. That is, thiouracilized patients manifest the involuting action without iodination of the hormone. Rawson et al. administered iodine in doses of 300 or more mgm daily to

thiouracilized patients and found that the iodine was not utilized for iodination or synthesis of thyroid hormone, nevertheless, the iodine effected involution of the hyperplastic glands of these patients. Before thiouracil was administered, the average mean thyroid cell height was 12.9 micra. After thiouracil treatment, the average mean acinar cell height was 13.9 micra, indicating a greater degree of hyperplasia. Iodine administered in conjunction with thiouracil caused a reduction in mean acinar cell height to 7.2 micra.

The studies of Rawson and his associates indicate strongly that iodine medication favorably counteracts certain effects of thiouracil — particularly the tendency toward hyperplasia induced by the goitrogenic drug. Again, diminution of the blood flow to and from the thyroid gland as a result of iodine treatment would seem to account for a reduction in the hyperplastic effect of thiouracil. This conclusion is in accord with the observation that the gland is markedly less vascular and that hemostasis is far more readily attained when iodine is used in conjunction with thiouracil than when thiouracil is used alone in preoperative medication of Graves' disease.

As Rawson et al. themselves stressed, in Graves' disease the thyroid gland rapidly takes up available iodine, the administration of which promotes the production of colloid material and presumably the manufacture of thyroid hormone. The avidity of the thyrotoxic gland for iodine is about two or three times that of the normal human thyroid. Nevertheless, iodine administration is followed by a decided fall in protein bound iodine (which includes thyroxine iodine). Although Rawson and his co-workers believed that their observations rendered untenable the hypothesis that iodine effects detoxication in Graves' disease by bringing about complete iodination of the hormone molecule, *the possibility still exists. Such iodination may occur but escape of the iodinated hormone (and perhaps some toxic iodine-containing molecule) is prevented by the increasingly edematous condition of the gland and the associated reduction in blood flow.* As Rawson and associates stated: "It is possible that the storage of thyroglobulin results from inhibition of some process which has to do with the increased rate of secretion of thyroid hormone. This process may well be retarded by slowed circulation."

Morton and his associates (1942), employing radioactive iodine as an indicator, found that the normal thyroid gland rapidly converts

labeled inorganic iodide to diiodotyrosine, and, further, that this conversion proceeds readily in the thyroid gland of rats subjected to hypophysectomy. The rate of formation of radio-thyroxin, however, is greatly depressed, according to these observers, in the thyroid after hypophysectomy. In 1946, Taurog Chaikoff and Bennett reported that the level of protein bound iodine in plasma falls as early as 48 hours after excision of the pituitary gland, these workers remarked that this finding was not surprising in view of the well known effects of hypophysectomy upon the morphology of the thyroid gland. More interesting was the observation that, whereas the protein bound iodine of plasma was decreased by as much as 55 per cent during periods up to a year after hypophysectomy, the thyroxin content of the thyroid gland did not fall below normal in a single instance, in some cases the amount of thyroxin in the thyroid was greater than normal. Taurog et al. concluded that a lowered thyroxin content of plasma and peripheral tissues is not a direct stimulation to the thyroid gland to release its thyroxin even though the thyroxin content of the thyroid may be greater than normal, the action of the thyrotropic hormone must be assumed to be clearly necessary for the release of thyroxin into the blood stream. These observations indicate at least 2 phases of thyroid activity are influenced by the thyrotropic hormone of the pituitary: the rate of formation of thyroxin and the rate of release of thyroid hormone in the blood stream.

The findings of Morton et al. (1942) and of Taurog and his collaborators (1946) are in accord with what we would expect, assuming that mechanical obstruction to circulation is a prime factor in the temporary amelioration of symptoms in patients with Graves' disease who have been treated with iodine preoperatively. The action of thyrotropic hormone on the thyroid gland would be less because (1) thyrotropic hormone reaches the thyroid in lessened amounts, and (2) the oxygen supply and supply of food and other essential factors to the thyroid are decreased — as results of the restriction in the blood flow. Further, the thyroxin content of plasma and peripheral tissues would be lowered if release of thyroid hormone (and, possibly, other iodine-containing compounds of a toxic nature) from the thyroid gland is retarded by such mechanical obstruction to circulation.

As we have remarked in an earlier section (page 122), the problem of the existence of more than 1 iodine containing thyroid secretion

has not been solved. Many authorities today believe that some toxic iodine containing secretion is produced in thyrotoxicosis. The most recent studies have shown that there are great physiological differences between various types of iodinated proteins.* We do not believe that the existence of more than 1 iodinated thyroid secretion can be ruled out in the consideration of the disorganized biochemistry and physiology of exophthalmic goiter. Another possibility which has not been given sufficient attention is the altered sensitivity of the hyperthyroid patient to iodine containing, thyroxin like proteins which may be produced in hyperplastic thyroid glands (exophthalmic goiter). It is well known that the hyperthyroid individual reacts differently to desiccated thyroid, the reactions of the euthyroid or hyperthyroid individual providing criteria of comparison.

Recent investigations of the effects of thiouracil and thiourea in thyrotoxicosis have given strong support to our early ideas on the nature of the action of iodine in preoperative treatment of the patient with Graves disease. During the first few years after the discovery of the value of such goitrogenic compounds in preparing the thyrotoxic patient for operation, it was thought by many writers that iodine medication could be dispensed with. Nevertheless it soon became obvious that the condition of the thyroid gland at operation is a vital factor. In thiouracilized patients not treated with iodine, at operation the thyroid gland is friable and bleeding is difficult to control. Means (1946), in his evaluation of the several methods of treating Graves disease which are available today, stated: "The use of thiouracil alone all agree, gives the surgeon a very vascular gland in which hemostasis is difficult." It is also evident that by giving both thiouracil and iodine together, one can achieve the nearly perfect operation. Not only is the patient in the euthyroid state, but the thyroid gland is inviolated and easy for the surgeon to deal with.

Such conclusions, which have been amply confirmed, and are now universally accepted, provide clear support for our theory of the action of iodine in preoperative medication of the thyrotoxic patient. The edematous condition of the iodine-treated gland explains the decreased friability and the readier attainment of hemostasis when iodine is administered in conjunction with thiouracil or thiourea. The back pressure

*An entire number of the *Journal of Endocrinology* (July 1945) was devoted to discussions of the various biological effects of different iodinated proteins.

caused by the rapid production of colloid material may be assumed to retard circulatory flow

Equally significant is the involuting action of iodine on the hyperplastic gland, as a result of iodine medication, the height of the acinar cells is decreased. Such a decrease in the height of the thyroid epithelium may be attributed also to the back pressure caused by deposition of colloid, diminution of the circulation must bring about a lessening of the activity of the thyroid epithelium after a week or two of iodine medication. Impairment of circulation means a reduction in the transport of oxygen and food factors as well as of stimulatory substances (such as thyrotropic hormone of the pituitary gland).

Iason (1915) has noted that the following features are of fundamental significance in iodine metabolism of persons with exophthalmic goiter: (1) thyroid gland iodine is below normal in untreated cases, (2) the blood iodine is generally above normal in untreated cases, (3) usually there is an increase in urinary excretion of iodine, and (4) there is a progressively decreasing iodine balance. In toxic nodular goiter there is a still greater excretion of iodine via the kidneys so that the negative iodine balance is even greater than in diffuse exophthalmic goiter. In noniodinized patients with toxic nodular goiter the blood iodine rises immediately after thyroidectomy, whereas in those patients treated with iodine, thyroidectomy is followed by a decrease in the iodine content of the blood. Iason thought it probable that hyperthyroidism results from an excessive discharge of the reserve iodine into the system, this discharge of iodine may be caused by the chemical decomposition, or disorganization, of the substance which normally serves to hold the iodine in storage. According to Iason the means by which iodine is normally set free from the thyroid gland is still unknown, as are the physiological and chemical roles of iodine in thyrotoxicosis. The response to iodine as observed in thyrotoxicosis does not occur in experimental hyperthyroidism in human beings or animals.

In their recent study of serum iodine in euthyroid subjects treated with desiccated thyroid, Riggs, Man, and Winkler (1915) observed that many euthyroid individuals differ from myxedematous patients in the ability to tolerate comparatively large doses of dried thyroid without exhibiting significant signs or symptoms of hyperthyroidism. Neverthe-

less, with the exception of goiter and exophthalmos, the chief features of Graves' disease as seen in the clinic were reproduced by the administration of dried thyroid in large amounts, to euthyroid subjects. Basal metabolic rate and serum precipitable iodine were increased, and serum cholesterol was decreased. Moreover, as in spontaneous hyperthyroidism, body weight declined, and the heart rate was increased, characteristic changes in total leukocyte count and in the relative portion of lymphocytes also occurred. There was a poor correlation between thyroid dosage and metabolic rate but excellent correlation between metabolic rate and level of serum precipitable iodine. Failure of basal metabolic rate to rise was regularly associated with a stable level of serum iodine, in the cases in which metabolic rate was significantly elevated after administration of desiccated thyroid, the serum iodine was also elevated.

The work of Riggs and co-workers, like many other studies of the effects of desiccated thyroid (or of thyroid hormone), cannot be said to prove more than that thyroid hormone has certain markedly stimulating influences on a number of physiological processes. Such determinations leave unsolved the problem of genesis of Graves' disease and would not seem to provide evidence for or against the theory that a toxic iodine-containing substance is produced in this disorder.

SIGNIFICANCE OF BLOOD IODINE LEVEL

Iodine enters the body chiefly from the digestive tract, although absorption through the skin may occur. The amount of iodine in the food and water influence the blood iodine content, as does the administration of iodine in medication. A number of investigators have noted that the blood iodine content rises during the summer months, presumably because of the higher iodine content of the diet at that season of the year. Part of the iodine present in the blood is in a form not excretable by the kidneys, but this form of iodine may be taken up by the thyroid gland, the liver and other tissues, where it is metabolized and passed back into the blood.

The blood iodine will be increased if there is a greater intake of iodine from the digestive tract (or through the skin), or if there is an increased output of iodine from the thyroid gland or other organs and tissues. This rise will persist only if the thyroid gland, liver and

other tissues are unable to take up and utilize the iodine normally, or, under certain conditions are unable to metabolize and dispose of supranormal supplies of iodine-containing substances

Because of the fact that the thyroid hormone contains iodine, it would seem natural that the iodine content of the blood would be increased in hyperthyroidism — provided of course, that the thyroid gland receives a continuous supply of iodine from the diet or other source. During the past few years, many of the studies on blood iodine have been made in an attempt to improve the diagnosis and to determine the results of various forms of therapy in thyroid disorders especially hyperthyroidism

More than a decade ago, a number of investigators reported that they found the blood iodine to be increased in practically every case of untreated hyperthyroidism (Curtis 1933, 1936, Schittenhelm and Eisler, 1932, Stern, 1933, Wohl, 1936). But these authors noted that there is no direct correlation between the basal metabolic rate and the iodine content of the blood. Schittenhelm and Eisler, who treated their cases of hyperthyroidism with x rays, stated that after the first treatment the blood iodine returned to normal or nearly normal levels, and as such treatment continued the iodine level varied between normal and subnormal. Yet in some cases the blood iodine became normal, although there was a lack of clinical response to treatment.

McCullagh (1935, 1936) found that the blood iodine was increased in most of his cases of hyperthyroidism but noted that in some instances it was within the normal range. In 1935, McCullagh reported that he had found the normal range of blood iodine in the Cleveland (Ohio) district to be from 6 to 9 micrograms (gammas) per 100 cc, however, he considered this range to be definitely low with the method of analysis used. In 1936, the McCullaghs stated that the normal average is from 8 to 12 micrograms. In 10 cases of active hyperthyroidism they found that the blood iodine ranged from 11.1 to 49.8 micrograms. Their tabulation showed no parallelism between the basal metabolic rate and the blood iodine. The patient with the lowest blood iodine (within the normal range) manifested the highest basal metabolic rate (plus 70) whereas the only other patient with as high a metabolic rate had a blood iodine content of 20.9 micrograms. These authors noted that it is more common to observe high basal metabolic rates with normal blood iodine than the reverse. Previously, Turner (1932) stated that

he found blood iodine values to be within normal range in 33.3 per cent of cases of hyperthyroidism.

In 1936, 2 reports from the Lahey Clinic (Perkin, Lahey and Cattell, Perkin and Cattell) noted that a considerable percentage of cases with clinical and microscopical evidence of hyperthyroidism may have blood iodine values within normal range, a blood iodine content of 10 gammas per cent being regarded as the upper limit of normal. In 174 cases of primary hyperthyroidism (exophthalmic goiter), the blood iodine levels ranged from as low as 2 to 149 gamma per cent, and 30 per cent of the group showed blood iodine within normal range. In 35 cases of adenomatous goiter with associated toxicity (secondary hyperthyroidism), 23 per cent had normal blood iodine (Perkin, Lahey and Cattell, 1936).

In the second report, Perkin and Cattell (1936) recorded that in 224 cases of hyperthyroidism (primary and secondary), the blood iodine values ranged from 2 to 155 gamma per cent, with normal values in 25 per cent.

It had been suggested by Lunde (1925) and again by Holst and Lunde (1929) that in hyperthyroidism the organic iodine or alcohol insoluble fraction rather than the total iodine of the blood is increased. Dodds and his associates (1932), using Lunde's method for the determination of the alcohol insoluble iodine of the blood, observed that this fraction is increased in patients with toxic goiter. In cases which are, however, clinically refractory to iodine treatment, the iodine fraction is reduced by the treatment, although the symptoms of toxicity persist and the basal metabolic rate remains high. Dodds remarked:

The conclusion is forced upon us that the alcohol insoluble fraction does not represent a measure of the toxic secretion by the thyroid.

Our own studies of blood iodine (DeCourcy, 1937, 1938) were undertaken with the hope of further elucidating phases of the problem of toxic goiter. With the method used, that described by Trevorrow and Fashena (1935), the normal blood iodine values in Cincinnati were found to range from 3 to 6 gamma per cent. Most of our cases of hyperthyroidism, it is true, showed an increase above these normal levels, but in a considerable percentage of instances the blood iodine was normal, and in the group as a whole no correlation was noted between the severity of the symptoms or the basal metabolic rate and the level of the blood iodine. In fact, as noted in reports before and since

the appearance of ours, some of the patients with normal blood iodine showed the most severe symptoms of thyroid toxicity. Such findings are of great interest in regard to the role of the liver in iodine metabolism and to the significance of blood iodine determination as a test of liver function (page 136)

Many of the early workers on blood iodine levels employed techniques which are now regarded as inadequate (Winkler, Riggs and Man, 1915). Determinations of serum iodine levels in apparently normal individuals as reported within the past few years are listed in Table 1

TABLE 1
Normal Concentration of Serum Precipitable Iodine
(protein bound iodine or hormonal iodine)

(according to recent reports)

<i>Authors</i>	<i>Normal Range of Serum Iodine (gamma per 100 cc)</i>	
Turner DeLamater and Province (1910)	6.7 to 16.7	(calculated from whole blood)
Riggs Gildea Man and Peters (1911)	4.0 to 7.0	(calculated from whole blood)
Salter Bassett and Sappington (1911)	1.0 to 8.0	serum precipitable iodine
Talbot Butler Saltzman and Rodriguez (1911)	6.0 to 8.1 (adults) 4.0 to 7.0 (children)	serum precipitable iodine serum precipitable iodine
Winkler Riggs and Man 1915	3.0 to 9.0	serum precipitable iodine

Note. According to Salter and McKay (1914) in human beings the normal concentration of hormonal iodine is approximately 3 micrograms per cent or 0.03 micrograms per cc. These authors reached this conclusion as a result of their own studies and a review of the literature.

Most authorities now agree that the blood iodine—specifically the protein bound fraction—is a sensitive index of circulating thyroid hormone (Salter, 1910, 1911, 1914, Riggs et al., 1912, Lowenstein et al., 1914, 1915, Winkler et al., 1916). Some authors extend this conception, to reach the conclusion that the serum iodine level is a reliable index of net thyroid function,* (Salter and McKay, 1914)—which must, however, be regarded as a generalization with a very significant percentage of exceptions. The exceptions noted in the earlier studies on blood iodine in hyperthyroidism have already been

mentioned. The newer studies have confirmed the previous findings that showed the frequently unreliable nature of blood iodine determinations — not only in hyperthyroidism but also in hypothyroidism and even in normal individuals (as reference to the wide range of values listed in Table 1 will prove). It seems necessary to assume that, in a great many cases of hyperthyroidism and in many hypothyroid patients some other factor (or factors) than thyroid activity must participate in important ways in iodine metabolism. We believe that the liver — and specifically the reticuloendothelial tissue of that organ — powerfully influences iodine metabolism both in the normal individual and the patient with a thyroid disorder.

Nevertheless, as a review of the recent findings on blood iodine make clear, determinations of blood iodine have important — and at times indispensable — applications in diagnosis and in the adequate control of therapy both for hyperthyroidism and hypothyroidism.

Perkin and Cattell (1940) have presented impressive evidence that the serum iodine level is a more reliable criterion than the basal metabolic rate in the differential diagnosis of *borderline* hyperthyroidism. Under carefully controlled conditions, 235 patients with *borderline* hyperthyroidism were studied by these workers. In the majority (*but not all*) of the patients for whom a tentative diagnosis of mild hyperthyroidism was not supported by later clinical observations, the blood iodine was not significantly elevated although the basal metabolic rate was generally above normal, similar findings were made in most of the cases of toxic goiter (nodular and exophthalmic) which were not benefited by subsequent thyroidectomy. Moreover, the blood iodine as well as the basal metabolic rate was elevated preoperatively and decreased postoperatively in patients who manifested clinical improvement following thyroidectomy.

Perkin and Cattell have also made use of the blood iodine content as an index facilitating the determination of the amount of thyroid tissue to remove; they have expressed the belief that employment of this index materially reduces the postoperative complications, hypothyroidism and recurrent hyperthyroidism.

Salter (1940, 1941), relying on blood iodine studies, concluded that Graves' disease may exist without physiologic hyperthyroidism. Salter (1940) has emphasized the value of blood iodine determinations in the differential diagnosis between hyperthyroidism and the following

conditions hypertension, cardiac decompensation, goiter without hyperthyroidism yet with an elevated metabolic rate

Curtis and Fertman (1945) have recorded additional evidence that analyses of blood iodine *but in conjunction with* determinations of basal metabolic rate are of value in a large percentage of cases in which differential diagnosis is difficult. They observed that the *average* blood iodine level is significantly above normal in all forms of thyrotoxicosis. The average blood iodine concentrations in exophthalmic goiter did not differ significantly from the average concentrations in toxic nodular goiter, this finding suggested the possibility that the nature or quality of the whole or fractionated blood iodine might differ in 2 different groups of patients. Here, once again, we encounter some suggestion of the possible existence of a toxic factor (unknown or X factor) in thyrotoxicosis, there being the further possibility that the toxic factor (if it does indeed exist) may have subtle differences in chemical and physiological nature according to the type of toxic goiter, exophthalmic or toxic nodular.

In non toxic nodular goiter, according to the work of Curtis and Fertman, the average blood iodine level is not elevated to any considerable extent, nor is it significantly elevated in non toxic diffuse colloid goiter. These investigators further observed a marked elevation in average basal metabolic rate in non toxic nodular goiter but not in diffuse nontoxic colloid goiter (in which the BMR averaged only minus 7 per cent).

Curtis and Fertman have pointed out the possibility that blood iodine determinations may be found to have some value in the diagnosis of ovarian struma, total intrathoracic goiter or other aberrant thyroid tissue which might otherwise be missed.

Clinically important observations involving blood iodine studies in hyperthyroidism and hypothyroidism have more recently been made by Winkler and others (1945, 1946) and Danowski and his associates (1946). Using improved techniques of blood iodine measurement, Winkler and co workers confirmed the frequently reported finding that characteristically although by no means invariably the level of precipitable iodine is elevated in untreated hyperthyroidism and tends to fall following iodine medication and thyroidectomy. Further they remarked on the rarity of supranormal values for serum iodine during the years following thyroidectomy for thyrotoxicosis and observed that

this finding supports the common belief subtotal thyroidectomy brings about a complete and enduring cure of hyperthyroidism in the great majority of cases. Nevertheless, their blood iodine determinations showed that mild or obscure postoperative hypothyroidism is of far more frequent occurrence than is generally believed. Winkler and his collaborators stated: 'Before the introduction of the serum iodine technique, diagnosis depended on clinical signs, on the basal metabolism and on the serum cholesterol. Since postoperative hypothyroidism is, more often than not, partial and clinically equivocal, all of these less sensitive indications may well fall within normal limits, thus rendering recognition difficult. These investigators, however, emphasized that the low rate of recurrences following the modern "radical" operation for thyrotoxicosis has fully justified the surgeon's present methods, more especially his judgment of the amount of gland to remove. On the other hand, the progress of the patient after operation should be carefully followed for months and years, repeated blood iodine determinations being made to disclose any marked degree of hypothyroidism not otherwise detectable. According to Winkler and his associates: 'A basal metabolic rate falling within the normal limits is no evidence that thyroid function is adequate. If hypothyroidism is not detected as it develops, the more severe grades may ensue—within a few months or after years—and the patient may be markedly affected before adequate treatment is sought or instituted.

Danowski and his co-workers (1946) have stressed the risks of hypothyroidism associated with (or following) therapy with thio drugs. They also based their studies on blood iodine determinations which were interpreted in the light of clinical observations. Their report has shown the high incidence of hypothyroidism which is a regrettable complication of thio-drug medication. Danowski et al. found that the decline in basal metabolic rate often lags behind the fall in serum iodine during treatment with thiourea or thiouracil. Even if the hypothyroidism is controlled by the administration of desiccated thyroid, a new danger arises—recurrent hyperthyroidism. According to the determinations of these workers, who based their conclusions on the blood iodine findings, thio drug therapy should at all times be supplemented with iodine medication. Blood iodine findings also demonstrated that the dosage of desiccated thyroid necessary to control hypothyroidism developing because of thio-drug therapy

varies from subject to subject, as would be expected, and lies between 0.03 and more than 0.06 grams daily.

The blood iodine levels, as shown by Danowski et al. as well as Winkler et al. (1945, 1946), indicate that each grain of desiccated thyroid effects an increase in serum iodine averaging 2 gamma per cent. Winkler pointed out that, even in the complete absence of hormone production by the thyroid gland, a final serum iodine concentration of about 6.0 gamma per cent — a level close to normal — should result from the administration of 3 grains of desiccated thyroid daily. This finding further indicates the approximate rate of production of hormone by the thyroid — an amount of hormone equivalent, in terms of iodine content, to 3 grains of U.S.P. desiccated thyroid per day. It must be cautioned, however, that a single subnormal serum iodine value is not diagnostic of a state of hypothyroidism (Riggs, Man and Winkler, 1945), and the appearance of slight symptoms of hypothyroidism does not necessarily establish that the thyroid is completely nonfunctional. Blood iodine levels must always be interpreted in the light of other laboratory tests and the complete clinical study of the individual patient.

Hence we may conclude that in a great many cases determination of serum iodine concentration is invaluable in diagnosis and in guiding therapy, whether with iodine, this drug or dried thyroid (as in hypothyroidism). Nevertheless, in many other cases, the serum iodine content may be misleading — in such instances we encounter low concentrations of serum iodine in severe thyrotoxicosis or high concentrations in hypothyroidism, or levels close to normal in either condition. Every report cited in regard to the significance of serum iodine content will be found to make mention or to emphasize the considerable percentage of exceptions to the general rule that blood iodine concentration is an index of thyroid activity.

IODINE METABOLISM IN RELATION TO LIVER FUNCTION AND THE RETICULOENDOTHELIAL SYSTEM

Blood iodine determinations have long been part of the routine examination of all cases coming to the DeCourcy Clinic. In the wide variety of diseases encountered, no important group has shown so consistently a supranormal blood iodine concentration as have cases of chronic cholecystitis and of liver deficiency (DeCourcy, 1937,

Stevens, 1937) The highest blood iodine values were observed in cases of chronic cholecystitis with stones in the common duct The next highest values were seen in carcinoma of the liver The values in other types of gallbladder diseases were lower, but still definitely above normal

It is generally recognized that the liver is to some extent damaged in all cases of gallbladder disease, but in cases with common duct obstruction and resulting biliary stasis the liver damage is especially pronounced The findings in regard to blood iodine suggest, therefore that the liver plays an important role in iodine metabolism and in the control of the iodine content of the blood Perkin and Cattell (1936), of the Lahey Clinic, also noted that in cases of gallbladder disease (acute and chronic cholecystitis and biliary obstruction with or without cholelithiasis) the blood iodine is usually increased, they commented that 'the relationship of liver function to iodine metabolism merits further study

The problem of the relationship of the liver to iodine metabolism has received comparatively little attention, although Maruno (1931) reported experiments indicating that the liver takes up iodine and excretes it into the bile, and that this function can be stimulated by injection of glucose and administration of certain galactogogues

Elmer and Luczynski (1933 1934) recorded experiments on rabbits showing that the iodine content of the bile is markedly increased after these animals have fed on iodine containing foods, but that the blood iodine is but little increased From these experiments it appears that the liver may play an important role in the regulation of the amount of iodine in the blood, as by removing any excess resulting from a high iodine intake in food or from other sources and excreting it into the bile where it is once more resorbed into the digestive canal (De Courcy, 1937)

These findings were confirmed by our own experiments on rabbits (DeCourcy, 1938), in which it was observed that in normal rabbits even when the iodine intake in the food is high, the blood iodine is never elevated much above the normal level for these animals But in animals in which common duct ligation or ligation and division of the duct has been done, so as to cause biliary stasis and jaundice, the blood iodine rises to a high level — in one instance it rose to 227 gamma per cent These experiments would seem to indicate strongly that the

liver has an important role in the regulation of the iodine content of the blood

That failure of the liver to function normally, rather than the excess of thyroxin in the blood, may account for the abnormally high blood iodine in many cases of hyperthyroidism is also suggested by the findings of Weller (1933). In a pathological study of 48 selected cases of Graves' disease in which no known cause of hepatitis could be found other than the possibility that it might be due to the thyrotoxicosis, well marked hepatitis was found in 54 per cent of the cases. In a matched control series, only one case manifested well marked hepatitis. *The lesions in these cases were irregularly distributed in the liver, and were characterized by a notable increase in the connective tissue, so that the liver lobules tend to be encircled by this increased fibrous tissue and isolated one from the other as in atrophic cirrhosis.*

More recently, Lord and Andrus (1941) recorded the following liver findings in patients with thyrotoxicosis, these findings being characteristic of all cases: (1) large fat droplets distributed diffusely through the parenchymal cells, (2) central necrosis of the hepatic cords, there being conspicuous infiltration of the necrotic areas by erythrocytes and polymorphonuclear cells, and (3) connective tissue proliferation in the portal areas, with lymphocytic infiltration.

McIver and Winter (1943) noted the hepatic damage resulting from anoxia induced after injection of crystalline thyroxin in doses sufficient to render experimental animals hyperthyroid. The histopathologic picture was featured by extensive necrosis of liver cells about the central area, there being some inflammatory cell infiltration in the portal areas. Fatty metamorphosis and engorgement of the blood vessels in the central areas constituted the earliest degenerative changes that were detected.

The changes in blood cholesterol content in thyroid disorders are familiar to all, and investigations in nutrition as well as in the field of thyroid pathology have served to establish the now indubitable relationship of blood cholesterol to liver function. The rise and fall of blood cholesterol in inverse ratio to the degree of thyroid activity represent as significant a feature of thyroid physiology and pathology as do the rise and fall of blood serum iodine in direct relation to intensity of thyroid activity. And, in the ultimate analysis, both blood cholesterol level and blood iodine level are to an important extent affected by hepatic func-

tion The relationship of liver function, thyroid disorders and blood cholesterol content have recently been emphasized by a number of investigators (Fleischmann and Schumacker, 1942, Peters and Man, 1943, Forbes, 1944, Simendinger, 1944)

Additional support of our theory that the liver participates fundamentally in the regulation of iodine metabolism comes from the findings of Scheffer (1933, 1934) that the iodine content of the feces is increased in hyperthyroidism These findings have been confirmed by Cole and Curtis (1935) Normally, the iodine content of the feces is small, the iodine being absorbed after being excreted into the digestive canal, but if the liver were removing an excess of iodine from the blood and therefore were excreting an excess with the bile, some of this excess would be likely to appear in the feces According to Scheffer (1934), the liver functions in just this way, exercising a detoxifying function in hyperthyroidism, that is, in hyperthyroidism there is an excess of iodine in the form of thyroxin, or a very similar compound, continually poured into the blood The liver removes this excess, and excretes it into the bile, which then passes into the gastrointestinal tract, so that some of the excess is discharged in the feces

If, then, the liver plays an important part in iodine metabolism, the question arises May this function be attributed to any of the special groups of cells of the liver? Maruno (1931) expressed the opinion that the parenchymatous cells of the liver are specifically the ones which take up iodine from the blood Yuzuriha (1933, 1935) recorded impressive experimental evidence indicating that the reticuloendothelial system is primarily if not exclusively involved in the metabolism of iodine His findings would appear to explain the relationship of the liver to the metabolism of iodine, the Kupfer cells of the liver being of course, an integral and active portion of the reticuloendothelial system

These experiments were carried out on rabbits Administration of an inorganic or organic iodine compound to normal rabbits caused a temporary rise in blood iodine, an increased excretion in the urine, and a deposit of iodine in the Kupfer cells of the liver and other portions of the reticuloendothelial system When the reticuloendothelial system was stimulated by a single injection of a small quantity of India ink, the metabolism of iodine was accelerated, as shown by a rapid

decrease of iodine in the blood a pronounced acceleration of its excretion in the urine, and decreased deposit of iodine in the reticuloendothelial system. If larger injections of India ink were repeatedly made until the reticuloendothelial system was blocked, the blood iodine remained high, its excretion was delayed, and heavy deposits of iodine were found in the reticuloendothelial cells of the liver and spleen. After thyroidectomy, the findings were the same as after blocking of the reticuloendothelial system with India ink and indicate that the loss of the thyroid inhibits the function of this system. When, however, a single stimulating injection of India ink was given after thyroidectomy, the result was much the same as in the normal animal, i.e., the iodine metabolism was accelerated and the level of blood iodine rapidly fell. The administration of powdered thyroid to thyroidectomized animals did not accelerate the iodine metabolism to the same extent as direct stimulation of the reticuloendothelial system. Repeated large injections of India ink blocked the reticuloendothelial system and prevented the restoration of iodine metabolism in the thyroidectomized animals despite the attempt to stimulate metabolism by administration of powdered thyroid.

The conclusions drawn from these findings are that the reticuloendothelial system and the thyroid gland act synergistically in the control of iodine metabolism, but even accelerated function of the thyroid fails to accelerate iodine metabolism if the function of the reticuloendothelial system is seriously impaired. On the other hand, if this system is directly stimulated, then iodine metabolism is accelerated even in the absence of the thyroid. This investigator believed that the reticuloendothelial system plays a dominant role in the metabolism of iodine and that the thyroid has only a secondary influence—that is, acts indirectly upon iodine metabolism by stimulation or inhibition of the reticuloendothelial system.

The significant percentage of exceptions to the generalization that serum iodine is an index of thyroid activity have been emphasized in the preceding section (on blood iodine levels). Our findings and those of others in regard to the participation of the liver and more specifically, the reticuloendothelial cells of the liver, appear to offer a logical explanation of these exceptions—which are so frequent and so marked as to necessitate the assumption that some factor, with a function as profound and as influential as that of the thyroid gland

itself, must be operative in both normal and abnormal metabolism of iodine

According to our theory, hyperthyroidism involves not just an excessive secretion of hormone by an overactive thyroid but also an overstimulation of the reticuloendothelial system, particularly the Kupfer cells of the liver, with consequent acceleration of iodine metabolism, so that iodine is removed more rapidly from the blood, the excess being excreted. When, however, the function of the reticuloendothelial system is inhibited, as it would be by hepatic lesions that diminish the activity of the Kupfer cells, then iodine metabolism as a whole would be inhibited, and blood iodine would be elevated. Even though the degree of hyperthyroidism was extreme with resultant severe symptoms of thyrotoxicity, a normal reticuloendothelial system would be stimulated so as to remove the excess hormone from the blood, thus would be explained the frequent finding of normal or nearly normal concentration of serum iodine in cases of marked thyrotoxicosis.

Further support for this theory is derived from the findings in leukemia, in which the functions of the reticuloendothelial system are often impaired—and in which the blood iodine is characteristically elevated. Finally, we have the evidence obtained from blood iodine studies in liver disease and in gallbladder disease with associated hepatic damage, although no hyperthyroid state exists; nevertheless the blood iodine level is generally supranormal.

Blood iodine determinations, therefore, would seem to be an index of liver function as well as of thyroid activity—rather than a mere measure of the latter. Frequently then, the finding of a high level of blood iodine indicates the need for measures to improve hepatic function and repair hepatic damage, the administration of glucose and the provision of a diet high in both carbohydrate and protein have been found highly beneficial.

The determination of blood iodine content in operative cases other than those involving the thyroid gland would, in view of the foregoing considerations, seem invaluable to ascertain possible liver damage, especially in patients with gallbladder disease because of the great danger of so called liver death. Blood iodine determinations do not require the introduction of a foreign substance as do certain other tests of liver function.

IODINE MEDICATION IN THYROTOXICOSIS

A few years ago, after the introduction of preoperative medication with thiouracil, thiourea, and other goitrogenic substances in Graves disease, it was widely stated that preoperative treatment with iodine had been outmoded. Nevertheless, as several times before in the history of the use of iodine in therapy of exophthalmic goiter, such a conclusion has turned out to be erroneous—because based upon false opinions as to the effects of iodine in this condition. The history of the utilization of iodine in goiter extends back through the centuries (see page 14, Chapter II). Not inconsiderable use of iodine in Graves disease was a fairly common procedure at the beginning of this century, but the pronouncement of the internationally famous Theodore Kocher in 1910 led to the almost universal abandonment of such medication, early misuse of iodine and overdosage, as well as misunderstanding of the nature of the reaction to iodine therapy in thyrotoxicosis, led to this warning of Kocher and similar pronouncements in the succeeding decade. The extended observations of Plummer (1923) again, and with irrefutable success, demonstrated the value of iodine administration to goitrous patients. Still, even today, doubts are expressed as to the wisdom of iodine administration and as to the dangers involved in such (preoperative) therapy of cases of Graves disease (Fitzgerald, 1941).

So once again, iodine therapy in exophthalmic goiter has been at last and entirely dispensed with, only to be restored to its former status as an indispensable aid to treatment. The value of iodine administration—even when thiouracil, thiourea and related compounds are given as the so-called main preoperative medication—has once more gained universal recognition.

It may be reaffirmed, as we pointed out more than a decade ago (DeCourcy, 1933), Of all therapeutic procedures for the cure of goiter subtotal thyroidectomy has proved by far the most efficacious. With improved technique we have succeeded in obtaining quicker convalescence and a lower mortality than formerly. The mortality has been less than 1 per cent in all cases. Of greater importance, however, has been the preoperative preparation of the patient with iodine. This preparation, we have found—and our findings have received ample confirmation—overcomes the greatest obstacle to successful

thyroidectomy, namely, the toxic phenomena and cardiac depression of exophthalmic goiter, which are so subject to aggravation by the emotional experience of the operation

Our practice has been to administer 10 minims of Lugol's solution three times daily for two to four weeks prior to operation, the dosage and period of preoperative medication depending upon clinical improvement and changes in the metabolic rate readings

With this treatment the patient improves progressively for 10 to 20 days. Nervous tension is relieved and apprehension is replaced by serenity. The symptoms of thyrotoxicosis gradually subside: tachycardia subsides, tremor abates, weight increases, and the basal metabolic rate falls toward the normal. In approximately 2 weeks, the patient who was formerly critically ill becomes comparatively well.

As experience has shown, this improvement is only temporary. If iodine medication is continued or stopped, no matter which, the patient suffers a relapse to his former toxic condition.

The point of the treatment, however, is that it enables us to improve a desperately sick patient to such an extent that he can stand the shock of a serious operation. Thus he becomes a much better surgical risk. The patient at this stage may be operated upon with safety and with little or no resulting reaction. On the other hand, if thyroidectomy is performed without previous iodine (or goitrogenic) medication, the postoperative reaction is frequently severe, the temperature rising to 106° or 107° with a fatal termination in many cases.

In our experience, nothing else contributes so much to lowered mortality from thyroidectomy as preoperative treatment carefully carried out. The aim is to operate at exactly the time when maximum improvement has been obtained. This may require 10 days of medication, or in some cases 3 weeks or longer.

Patients operated upon while they are saturated with iodine do not suffer severe postoperative reaction. We feel no apprehension in operating upon a subject who has been treated adequately beforehand with iodine.

It has been our practice in operating on cases where iodine has been given over a long period, but in which toxic symptoms are still manifest, to give $15\frac{1}{2}$ grains of sodium iodide intravenously immediately after operation—while the patient is still in the operating room. Fifty minims of Lugol's solution are administered by rectum as soon as

the patient returns to bed, and this procedure is repeated in eight hours. If the temperature rises above 102° on the following day, Lugol's solution is given by mouth every 4 to 6 hours.

It is very important, as a prophylactic measure, to continue treatment after operation until all danger of a secondary reaction is past. It is our practice to give 10 minims of Lugol's solution daily for 8 weeks after the postoperative reaction.

Various opinions have been expressed as to the value of suspending iodine administration when uncontrollable conditions have necessitated the prolongation of such medication beyond the usual period, possibly for many weeks when the patient does not appear to be operable. It would seem wise, under such circumstances to keep the patient in the hospital and wait for some remission at which time operation may be performed with a sufficient margin of safety. Exceptionally, in such severely thyrotoxic patients, a rest period of some weeks — suspension of iodine medication — may be indicated.

Most authorities agree, that after iodine therapy and before operation is performed, the basal metabolic rate should be less than 50 per cent higher than normal — but as must be emphasized basal metabolic rate is by no means a sure indication of the degree of thyrotoxicity in a given patient. Its determination is of value when other factors — such as the clinical picture and the blood iodine (serum iodine) — are taken into consideration at the same time. The significance of serum iodine is discussed at some length in a later section (page 308). Patients with a basal metabolic rate of more than 50 per cent above normal must be considered as definitely poor operative risks, such a high metabolic rate may be assumed to be indicative of a severely toxic condition. In the average patient, as the symptoms show improvement, the basal metabolic rate falls 20 to 50 per cent as a result of iodine medication.

Most clinicians hold that cases of nodular goiter with toxicity respond more slowly to iodine therapy, not only is the response less marked but it is also less certain. Many authors have expressed the conviction that administration of iodine to patients with toxic nodular goiters may result in an exacerbation of symptoms.

In a recent review of the dangers of the incorrect use of iodine in the treatment of goiter, Fitzgerald (1944) stated that there are three types of patients in whom iodine thyrotoxicosis seems to have been

induced (1) goiter in adolescence, (2) cases of exophthalmic goiter receiving iodine medication during a prolonged period, and (3) cases of nodular goiter. This writer concluded that iodine therapy should be reserved strictly for cases of diffuse goiter with toxicity.

Some 3 per cent of patients with Graves' disease do not respond favorably to iodine therapy (Means and Lerman, 1931). In practically all patients, continued use of iodine past a period of 4 to 5 weeks must be expected to cause an intensification of symptoms. Discontinuance of iodine therapy, on the other hand, is followed by a worsening of the condition of the thyrotoxic patient, the basal metabolic rate rising and the general symptoms approximating in their severity those existing before medication was begun. It is true that many cures have been reported to occur as a result of iodine therapy alone in exophthalmic goiter, but most observers have found that if such cures do eventuate they are exceptional. In this connection it must be remembered that spontaneous remissions do occur and that numerous instances of this type of outcome (burned out thyrotoxicosis) have been recorded. We have all seen cases, unoperated, which have subsided, to leave only slight exophthalmos as evidence of the former condition.

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CHAPTER VI — B

THIOURACIL, PROPYLTHIOURACIL AND RELATED DRUGS IN TREATMENT OF THYROTOXICOSIS

ANTITHYROID DRUGS

IT HAS BEEN known for many years that hypertrophy and hyperplasia of the thyroid gland can be produced in animals by diets high in certain plant materials. In 1928, Chesney, Clawson and Webster found that when cabbage is fed as a major portion of the diet, goiter develops in rabbits. Later, it was shown that hyperplasia of the thyroid is produced in rats by feeding *Brassica* seeds (Hercus and Purves 1936). Kennedy (1942) reported that the probable causative factor supplied by these seeds is allylthiourea, and, further, that thiourea is actively goitrogenic. A large number of substances chemically related to thiourea were tested by Astwood and co workers (1943) and thiouracil was found to be the most actively goitrogenic. Confirmatory studies were reported by MacKenzie and MacKenzie (1943). Besides the thioureas, a number of other groups of compounds have been shown to be goitrogenic: cyanides, thiocyanate, and sulfonamides (especially sulfadiazine). Patients receiving thiocyanate in the treatment of hypertension have frequently been reported to develop goiter (Foulger and Rose, 1943).

Investigations inspired by these findings have demonstrated that only an indirect effect of these substances is involved in the production of hypertrophy and hyperplasia of the thyroid — their goitrogenic effects are not observed in hypophysectomized animals. Recent researches have apparently established that the enlargement of the thyroid is the result of increased secretion of thyrotropic hormone of the pituitary. The feeding of thiourea depresses the oxygen consumption of the intact animal but does not inhibit the calorigenic action of administered thyroxin or desiccated thyroid. It must be concluded that thiourea and other goitrogenic substances which have been investigated act so as to depress

the production of thyroid hormone. Hence the clinical use of thiourea and especially thiouracil was suggested (Astwood, 1943, Williams and Bissell, 1943). Even though these substances increase the work of the thyroid gland—as evidenced by the marked hyperplasia and hypertrophy following their administration—they must be regarded as 'antithyroid' drugs inhibiting the function of the gland.

THIOUREA

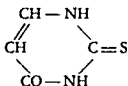
Thiourea has the chemical structure



Although it has been used clinically in a limited number of cases, this drug has been found unsatisfactory as compared with thiouracil. The antithyroid activity of thiourea is not as great as that of thiouracil. Moreover, thiourea causes more gastrointestinal disturbances and gives the breath an unpleasant odor.

THIOURACIL

The structural formula of thiouracil is



The substance is a fairly stable, white powder, only slightly soluble in water and insoluble in alcohol, but readily soluble in sodium hydroxide solution. Although odorless, it has a bitter taste.

Effects on Animals As shown by histological examination of the thyroid gland, effects following the administration of thiouracil include the production of tall columnar acinar cells, marked hyperplasia, a diminution of colloid, and increased vascularity. Relatively little iodine (administered as a dose) is absorbed by the gland, and the contents of both iodine and thyroxin are diminished as is the basal oxygen consumption. Thyroxin production is reduced. Because thiouracil does not stimulate goiter formation in hypophysectomized ani-

mals, it would seem definitely established that the pituitary gland is involved in the action of the drug. The histological changes in the pituitary are similar to those after thyroidectomy. Growth of young animals is retarded by prolonged administration of thiouracil. In general, the effects of thiouracil administration (for several weeks to several months) are very like those resulting from subtotal thyroidectomy.

Effects in Human Beings As in animals, the effects of thiouracil administration include the production of cellular hyperplasia of the thyroid, diminished colloid, and increased vascularity. Nevertheless, thiouracil at the dosage levels usually administered to human beings with thyroid disease does not as a rule induce a marked increase in the size of the gland, such increases as have been observed are transient in most cases. An eventual reduction in the size of the gland has frequently been noted. The consensus is that the hyperplasia produced by thiouracil results from stimulation by the thyrotropic hormone of the anterior pituitary, because the production of thyroxin by the thyroid has been inhibited, presumably the formation of thyrotropic hormone is increased.

Studies with radioactive isotopes of iodine have shown that the thyroid gland of an individual treated with thiouracil stores very little iodine. Further, the thyroxin content as a rule is extremely small. Bioassays have disclosed that, after treatment with the drug, calorogenic activity is at a minimum or entirely absent.

Absorption, Distribution and Elimination The absorption and elimination of thiouracil and its distribution in the body fluids and tissues have been carefully studied by Williams, Kay, and Jandorf (1944). These workers found that thiouracil is absorbed rapidly from the stomach and upper portion of the small intestine. Substantial concentrations of the drug appear in the blood within 15 to 30 minutes. Approximately 15 per cent of a therapeutic dose is apparently destroyed before or during absorption. No thiouracil is detectable in the feces following administration of such a dose.

The concentration in the blood ranges between one and six milligrams of thiouracil per 100 ml. for 2 or 3 hours after absorption. Pleural fluid and ascitic fluid contain about the same quantity of thiouracil as does blood, relatively small amounts being present in cerebrospinal fluid, pericardial fluid, and edema fluid. Most of the

circulating thiouracil is found in the red blood cells. To maintain satisfactory levels in the blood, the quantity given daily should be divided into three doses because thiouracil rapidly disappears from the blood. The highest concentrations in the tissues are present in the thyroid, the pituitary, the adrenals and bone marrow (leukocytes), various lesser concentrations are found in the other body tissues. About 50 per cent of the administered thiouracil is rapidly destroyed in the tissues, almost all of the drug has disappeared after 24 hours. The remaining portion about 35 per cent of the dose, is excreted by the kidneys (15 per cent being destroyed before absorption). Most of the thiouracil excreted appears in the urine within a few hours after absorption.

The liver does not appear to be the main site of thiouracil destruction, the blood level after a test dose is no higher in patients with advanced cirrhosis of the liver than in normal individuals. The substances produced by the breakdown of thiouracil have not been identified. After administration of the drug, there is an increased excretion of neutral sulfur but no increase in the excretion of thiourea, cystine, cysteine, thiocyanate, thiosulfate, urochrome or melanin. Nor does uracil appear in the urine.

Although patients with severe damage to the kidneys excrete only small quantities of thiouracil, their blood thiouracil level after a test dose is no higher than in the case of normal individuals.

The administration of thiouracil to pregnant and lactating women is contraindicated, we believe, by the observation that the drug passes readily through the placenta and also is found in comparatively high concentration in the milk of lactating mothers.

Thyroid Tissue after Thiouracil Therapy. The appearance of thyroid tissue removed from thyrotoxic patients after treatment with *thiouracil (over a prolonged period)* is similar to that of tissue from a non-iodized toxic goiter although there is a tendency toward more hyperplasia and less colloid in the instance of the former. In some patients an increase in hyperplasia is observed when sections from the same gland before and after therapy with thiouracil are compared. Typically, after thiouracil treatment, the gland has a varied appearance, the sections differing considerably. Very tall columnar epithelial cells are commonly noted, along with many papillary projections and very little if any colloid. Apparently solid sheets of cells may be encountered

in some areas, the acinar structure being difficult to discern. In other areas, the hyperplasia is less and there is somewhat more colloid. Usually, a marked increase in vascularity is observed.

Clinical Response to Thiouracil Therapy According to Williams and associates (1943, 1946) and other leading authorities on the use of thiouracil in the treatment of hyperthyroidism, as a rule improvement is marked within 1 week and becomes more pronounced during the latter part of the first month of therapy. Indeed, it has been claimed that few if any symptoms or signs of thyrotoxicity persist after 5 to 6 weeks. Many of the more favorable reports state that the tremor, cutaneous changes, tachycardia, palpitation, dyspnea and diarrhea disappear in most cases, nervousness is alleviated, the appetite improves, and the patient puts on weight. Although the non malignant type of hyperthyroidism is decidedly benefited within the first month of treatment, the malignant type of exophthalmos increases in severity.

No appreciable change in consistency or size of the thyroid gland is to be expected during the first 6 weeks of thiouracil administration. There may be no detectable changes in the glands of some patients after months of therapy with this drug, in other patients the gland may become both larger and firmer, whereas in still other cases its size is somewhat reduced and it becomes softer. In certain instances glands having a size 3 times normal may eventually show a fifty per cent reduction in size, to remain indefinitely $1\frac{1}{2}$ times normal size. Such a decrease in the size of the thyroid is, however, by no means a general finding. Many observers have remarked that an actual increase in size is the characteristic result. While changes are occurring in the thyroid gland a few patients may complain of pain in the thyroid region.

There is a progressive decline in the basal metabolic rate, the normal level generally being attained within 2 to 7 weeks, the average length of time required for the basal metabolic rate to fall within the normal range is 5 weeks. Sometime within the first 2 months of therapy the blood cholesterol also usually approximates the normal level. Continued thiouracil administration (minimum dosage) may be expected to maintain normal basal metabolic rate and clinical remission indefinitely. The longer the period of thiouracil therapy, however, the more likely is the development of toxic effects.

When, after a month or two, thiouracil administration is discontinued, a relapse may occur within a period of from 2 weeks to about

a month Toxic effects are more frequently observed during a second course of treatment than during a prolonged period of constant, daily administration of the drug If thiouracil therapy has been continued for more than 6 months, remission of symptoms may endure longer than 3 months The data available at present indicate that no cures have been attained, relapses eventually occur even after treatment for more than a year

In most cases, thiouracil has been used only in preparation of the patient for thyroidectomy The drug brings about a complete remission of the symptoms preoperatively in a larger proportion of cases than does iodide therapy As a rule (not without many exceptions), patients treated preoperatively with thiouracil (alone) experience less cardio-respiratory distress during the operation than do patients treated with iodide, the postoperative course is usually smoother and shorter Not only is the patient likely to be quieter, but also the tendency to develop fever and tachycardia is less Further, the use of thiouracil has greatly reduced the number of 2 stage operations

On the other hand, the percentage of cases in which thiouracil manifests toxic side effects is comparatively high (see page 156) Besides the drug often markedly increases operative difficulties After thiouracil treatment, the gland becomes more friable and bleeds more readily Occasionally, *perithyroiditis* is associated with thiouracil therapy and adds to the technical difficulties

Effect of Previous Iodide Therapy Iodide treatment during a period of 6 weeks or longer preceding thiouracil treatment causes a retardation of response to the latter, as evidenced by a slower reduction in basal metabolic rate and a slower general improvement in clinical condition Iodide therapy, however, has been used by some surgeons as an adjunct to thiouracil therapy, the purpose being to lessen the technical difficulties at operation

Dosage Thiouracil is usually provided in tablets of 0.1 Gm. each In early work with thiouracil therapy of patients with hyperthyroidism unnecessarily large doses — 1 Gm., or ten 0.1 Gm. tablets, per day, or even larger quantities — were tried More recent investigations have established that much smaller doses are as effective and, at the same time, are probably much less toxic All extensive studies thus far reported suggest the use of not more than 0.4 Gm. of thiouracil per day at the institution of therapy We are convinced that the dosage

should never be in excess of this quantity. Divided doses — 3 or 4 times a day — tend to maintain a higher level of thiouracil in the blood (and the thyroid) and are more effective than a single dose. After 2 weeks of such daily dosage, the amount administered should be reduced to 0.2 to 0.3 Gm per day. After the basal metabolic rate has been brought within the normal range, the generally recommended dosage is 0.1 or 0.2 Gm daily.

It is the consensus that administration of thiouracil 3 times a day leads to a quite satisfactory response and therefore is practical, although it may be true that, to obtain ideal therapeutic levels of thiouracil in the blood and thyroid, the drug would have to be administered every three hours throughout the 24

The dosage does not directly determine the concentration of thiouracil in the tissues of the thyroid. In patients on the same dosage, the level of thiouracil present in the thyroid tissues of the thyrotoxic patient varies widely — and the response is different in different patients. No correlation has been observed between the response of the thyrotoxicity and the concentration of the drug in the gland tissue. In euthyroidism, as a matter of fact, a larger amount of thiouracil is necessary to obtain a given level of the drug in the thyroid than is the case in hyperthyroidism. When potassium iodide is administered along with thiouracil, the therapeutic level of the latter is not increased (Bartels, 1945a).

Synergistic Agents As we might expect, the tendency to excessive hyperplasia of the thyroid and the development of exophthalmos and other ocular disturbances to be expected from the action of thyrotropic hormone — as its production is increased by thiouracil — may be prevented by small doses of desiccated thyroid or thyroxin (Palmer, 1945). According to Bartels (1945a), iodide therapy in conjunction with thiouracil probably diminishes to some extent the surgical difficulties (especially the tendency of the gland to bleed more readily after thiouracil therapy).

Duration of Preoperative Medication Because of the frequency of delayed response to thiouracil therapy, especially in patients previously on iodine, medication may be continued for at least 30 days before it can be concluded that the previously iodinated patient will not respond to the drug, thiouracil may have to be administered during a period of perhaps 4 months (Van Winkle et al., 1946).

Toxic Effects. Many investigators believe that the incidence of adverse reactions in thiouracil therapy of thyrotoxicosis has been somewhat less than the incidence of complications from the more extensively used methods of treatment (Van Winkle et al, 1946). Nevertheless the incidence of adverse reactions may be as high as 10 to 13 per cent, and death attributable directly to the drug has been reported to occur in about 0.5 per cent of cases, the incidence of fatalities during the administration of the drug being about 0.73 per cent, according to 1 survey (Moore et al, 1946). Hence every patient under treatment with thiouracil should be closely followed, extreme care being necessary.

The most serious complication is granulocytopenia which may be expected to occur in about 2.5 per cent of all cases treated with thiouracil, according to a questionnaire survey comprehending the results of treatment of 5,715 patients by 328 clinicians (Van Winkle et al, 1946). This toxic manifestation most frequently occurs during the first 3 months of treatment, 80 per cent of cases having been encountered during this period. Occurrence of granulocytopenia could not be correlated with the dosage level. In the survey of Van Winkle and co-workers, a diagnosis of granulocytopenia was accepted when (1) the total white count fell below 4,000, (2) the granulocytes were diminished, and (3) such changes in the blood picture were accompanied by the sudden onset of acute symptoms including fever, sore throat, and prostration. It is difficult, however, to distinguish between simple neutropenia and malignant granulocytopenia in its early stages. Agranulocytosis may appear without warning, and it has been noted that even frequent blood counts may not serve to detect satisfactorily the onset of this toxic manifestation. It is important to teach the patient to recognize the symptoms which may indicate the beginning of the condition (Moore et al, 1946). Every patient must be instructed to omit the drug and report immediately to the physician in the event of the development of sore throat, coryza or any febrile illness. When the complication does set in, massive doses of penicillin (500,000 units per day) may be found effective. The risk of transfusion reaction would seem to rule out the suggestion that repeated transfusions of small quantities of whole blood be carried out. Resumption of thiouracil therapy after a lapse seems to predispose the patient

to agranulocytosis. We would like to stress the fact that, although most cases of agranulocytosis develop during the early weeks of thiouracil treatment, the complication may appear at any time.

Leukopenia comprised one third of the all toxic reactions reported in the survey of Van Winkle et al., this complication of thiouracil therapy having an incidence of 4.4 per cent. Sixty per cent of cases occurred during the first 4 weeks of treatment, and 75 per cent had developed by the end of 8 weeks. Still, the complication may manifest itself suddenly at any time, just as in the instance of granulocytopenia. We agree with other conservative authors that the appearance of this complication is an imperative indication for discontinuance of thiouracil. Hospitalization would seem essential if there is a decided reduction in granulocytes. The relationship between granulocytopenia and leukopenia as toxic manifestations of thiouracil administration remains obscure. The probability of the occurrence of leukopenia is apparently increased by sulfonamide therapy.

Skin reactions have been reported to constitute one fourth of the adverse reactions to thiouracil, an overall incidence of 3.3 per cent was recorded by Van Winkle et al. These reactions are decidedly varied and usually mild. The most frequently observed skin reaction was urticaria. Because similar dermatoses have been associated with more severe reactions to sulfonamide administration, the continuance of thiouracil therapy subsequent to the appearance of such symptoms would seem to be unwise.

Drug fever may be expected to occur in some 3 to 5 per cent of cases (Moore et al., Van Winkle et al.). Van Winkle and his associates found that about 85 per cent of such reactions are encountered during the first 4 weeks of thiouracil administration. In some instances, temperatures ranging up to 106° F. were recorded. It is to be remembered that fever is a symptom of agranulocytosis, hence in the event that the patient develops a fever, agranulocytosis must be ruled out by immediate white blood cell and differential counts.

Many other toxic reactions to thiouracil have been reported in the literature: lymph node enlargement, swelling of the lacrimal and salivary glands (Bishop and Rawson, 1946), conjunctivitis, edema of the feet, liver damage, jaundice, psychotic manifestations, purpura, anemia. Occasionally, as a result of overly prolonged treatment with thiouracil,

mild to profound myxedema has been observed. At operation under such conditions the hypersensitivity of the myxedematous patient to opiates must be kept in mind.

Theoretical Possibility of Carcinogenesis It has been demonstrated by Bielschowsky (1944) that thiouracil administered together with a carcinogenetic chemical (for instance 2 acetaminofluorine) induces the development of malignant tumors of the thyroid. The possibility is therefore suggested that the hyperplastic tissue of the thyroid in human cases to whom thiouracil is administered may also give rise to malignant tumors provided some synergistic carcinogen (intrinsic or extrinsic) exerts its effects at the same time.

Adenomas are found in a high percentage of thyroid glands in older patients with toxic diffuse goiter. Further, some 3 to 8 per cent of grossly adenomatous goiters have been reported to show definitely carcinomatous changes. Occasionally, also, even in hyperplastic thyroids neoplasms may be revealed by histologic study to be present in small adenomas. Careful and extensive investigations would seem indicated to determine if possible whether or not thiouracil may adversely influence the dyscrasia which results in adenomas and carcinoma *in situ* in a great many thyroids. Will prolonged administration of thiouracil cause clinical cancer in the older patient? The problem has been set forth by several thoughtful authors, but no evidence has been forthcoming as yet.

Thiouracil in Hyperthyroidism Associated with Functioning Metastases of Adenocarcinoma In 2 cases of adenocarcinoma of the thyroid with functioning metastases and hyperthyroidism, thiouracil produced a complete remission within a few weeks—as shown by the effects on the patients' general condition, basal metabolic rate, plasma cholesterol, body weight and blood iodine (Leiter et al. 1946). Previous iodization had resulted only in aggravation of the condition. According to Leiter and his associates, thiouracil can suppress hormone production in metastases of adenocarcinoma of the thyroid just as readily as the drug inhibits this process in the hyperplastic gland of ordinary Graves disease.

Thiouracil in Acute Thyroiditis King and Rosellini (1945) have reported favorable results with thiouracil in the treatment of thyroiditis. These workers administered moderate doses of the drug to 7 patients with acute thyroiditis, 3 patients with migratory thyroiditis

and 1 patient with struma lymphomatosa (Hashimoto's struma). The process in all 7 patients with acute thyroiditis and 1 patient with migratory thyroiditis had had a duration of 3 weeks or less, all of these were symptom free after 1 week on thiouracil. In one case of migratory thyroiditis the drug was not tolerated and had to be discontinued. Of the remaining 3 patients who did not respond to thiouracil 1 had previously been given a diagnosis of toxic goiter and had taken 10 drops of Lugol's solution 3 times a day for 3 months. This patient made little improvement on thiouracil. Another patient had been treated 5 months previously with x rays and was past the inflammatory stage. No improvement resulted from 3 weeks treatment with thiouracil. The remaining patient had previously received a diagnosis of toxic goiter and had been treated with iodine. Histological examination of the gland after operation established the diagnosis of Hashimoto's struma, also hyperplasia had apparently been produced by thiouracil therapy. The authors believe that thiouracil is of benefit in the acute stage of thyroiditis.

THIOBARBITAL

Astwood (1945) reported that thiobarbital (diethyl thiobarbituric acid) has somewhat greater antithyroid activity in rats than does thiouracil, small doses seemed to be more effective in inhibiting thyroid function and apparently were less toxic than corresponding doses of thiouracil. Fatty infiltration of the liver results from the administration of large doses of thiobarbital. Subsequently Astwood and his associates (1945) and Bartels (1945b) reported on the use of thiobarbital in clinical hyperthyroidism. Bartels observed toxic reactions in 28 per cent of all patients receiving the new drug and therefore stated that it should be used only in patients who have toxic reactions to thiouracil. When thiobarbital could be administered without producing toxic reactions, it appeared that response to this antithyroid substance was similar in every respect to response to thiouracil. The dosage recommended by Bartels is only 0.05 Gm daily so that the antithyroid activity of thiobarbital appears to be 12 times that of thiouracil. We believe, however, that thiobarbital is far too toxic to find extensive clinical use.

6-ISOBUTYL THIOURACIL

Williams (1946) has reported that 6 isobutyl thiouracil is more than 20 times as goitrogenic as in thiouracil in rats. Tests with this new antithyroid drug on 36 patients indicated that it is less toxic than thiouracil. Obviously, however, extensive studies must be carried out before we can determine whether or not 6-isobutyl thiouracil is as effective as and safer than thiouracil.

CONCLUSIONS SUGGESTED BY AVAILABLE DATA

On the basis of the information available at the present time we agree with the majority of other clinicians that thiouracil is undoubtedly effective in the management of thyrotoxicosis and may ultimately be found to have some value in the treatment of thyroiditis. Even if thiouracil is replaced by some safer antithyroid drug its introduction represents an important advance at least in the preoperative treatment of cases which have become iodine-fast and in therapy where thyroidectomy is contraindicated. We believe it to be obvious that thiouracil is valueless and contraindicated in other thyroid disorders — it should not be used in conditions which are not associated with hyperthyroidism. Van Winkle and his co-workers have stated (1946). The wisdom of depending on thiouracil as a substitute for operative procedure can be determined only by following the results of investigations carried on for longer periods. The data now available in the literature establish in our opinion that the incidence of severe toxic reactions is distinctly high enough to rule out the extensive substitution of thiouracil therapy for (ultimate) thyroidectomy in thyrotoxicosis. As evidence strongly supporting our view we may cite the following facts: (1) supervision of the patient receiving thiouracil must be indefinitely prolonged, extremely careful and therefore often excessively tedious; (2) no cure of thyrotoxicosis has yet been claimed to result from thiouracil therapy; (3) a fatal agranulocytosis may develop suddenly at any time; (4) the incidence and severity of hepatic damage caused by thiouracil administration would seem to have been underestimated (Moore 1946); (5) the possibility of carcinogenic action, particularly in the patient past middle age, remains largely uninvestigated (Editorial 1945b), and (6) thiouracil is effective primarily because of the changes (in physiology if not fundamental histology) it induces

in the pituitary, the grand integrator of endocrine functions. No studies on the relation of thiouracil administration to longevity have been reported. And the latent effects of the drug may eventually turn out to be far more dangerous than the early toxic effects emphasized at present. We believe it highly significant that some of the investigators who have had the most extensive experience both with thiouracil therapy and basic research (experimentation on animals) not only have of late been seeking less toxic antithyroid substances but also have introduced safer congeners of thiouracil into clinical practice (Astwood, 1946, Williams, 1946). Hence, in common with many other authors, we look forward to the finding of a more satisfactory antithyroid drug than thiouracil. Certainly, caution is indicated in the meantime.

Thus, because the juvenile and other mild types of hyperthyroidism can generally be controlled quite successfully by iodine therapy alone, thiouracil is definitely contraindicated in these forms of hyperthyroidism except in the small percentage of cases unresponsive to iodide.

Further, the use of the drug in the malignant type of exophthalmic goiter appears to be beset with too many complications to justify this mode of treatment. The continued use of thiouracil in those cases which manifest the less severe toxic reactions is advocated by some but seems to us quite inadvisable.

Of course, the remarkably favorable results obtained in a certain percentage of cases naturally suggests mass use of thiouracil therapy in hyperthyroidism. Nevertheless, the high incidence of known toxic reactions and the ever present potential dangers demand such careful and prolonged supervision of every patient as to make previously established procedures (iodide therapy and thyroidectomy) seem quite simple and, all practical factors considered, safer in comparison.

PROPYLTHIOURACIL FOR THYROTOXICOSIS

After testing hundreds of antithyroid substances, Astwood and VanderLaan (1946) found that propylthiouracil is not only highly effective but also apparently the least toxic thio drug yet investigated. Because of the eminently satisfactory results obtained in preliminary studies, Astwood and VanderLaan were encouraged to employ propylthiouracil in the treatment of 100 selected cases of thyrotoxicosis. These patients were encountered during the course of 1 year and were

treated with propylthiouracil for periods ranging from 3 to more than 6 months. Considerable variation in the minimum effective dose was observed, but careful studies of the progress of the patients led Astwood and VanderLaan to the conclusion that 50 mg. of propylthiouracil every 8 hours probably represents the optimal dosage level for the routine treatment of the more severe cases. Milder hyperthyroid cases were found to respond satisfactorily to doses of 50 mg. twice daily. Astwood and VanderLaan recommended that an effective dose should be continued until all manifestations of the disease have been controlled before smaller maintenance doses are substituted. Some patients did not show the desired improvement until after many weeks of therapy with the higher dosage. Further, these workers have stressed the point that the routine employment of propylthiouracil at dosage levels above those used in their investigations should await extensive clinical studies on the safety of the administration of larger quantities of the drug.

The outstanding observation in the study of Astwood and VanderLaan (and in studies now in press) was that no significant side effects whatsoever resulted from the use of this new thio drug.

In view of the numerous toxic side effects of thiouracil — which, as Astwood and VanderLaan remarked, have caused many to shun even the name of the drug — the apparently complete lack of untoward reactions in propylthiouracil therapy is indeed remarkable. Nevertheless, these investigators have cautioned. Doubtless some sensitivity reactions will be encountered if this compound is extensively employed. There are a few drugs which when continually administered do not provoke untoward reactions in a certain percentage of individuals. It is also true that sufficient time has not elapsed to determine whether or not some late-appearing or insidiously developing toxic effect may follow the use of propylthiouracil. All thio drugs effect changes in the pituitary.

Although no true *side effects* were noted by Astwood and VanderLaan, their report shows that considerable danger of the production of a severe hypothyroid state is associated with propylthiouracil therapy. Incipient hypothyroidism was detected in a number of cases. Three patients manifested clear clinical evidence of hypothyroidism or an excessively elevated serum cholesterol after being given 150 mg. daily, for 2½, 4 and 5 months, respectively. Two patients developed hypo

thyroidism from 100 mg of the drug daily, 1 from 50 mg daily, and still another from 25 mg daily. Astwood and VanderLaan observed the following symptoms of excessive dosage: lethargy, excessive gain in weight, pasty and puffy facial appearance and conspicuous enlargement of the thyroid gland. Moreover, they believed if larger doses than 150 mg daily are used in the future the incidence of myxedema will probably be troublesomely high unless careful and frequent examinations of the patient are not carried out.

Several of the larger clinics have already stopped the use of thiouracil and have instituted routine therapy with propylthiouracil. This trend will, in all probability, continue. Taking into consideration not only the probable development of hypothyroidism but also the high percentage of relapses following the use of any antithyroid drug in thyrotoxicosis at the present time the conservative opinion would seem to be that antithyroid medication should be merely a preoperative measure. Subtotal thyroidectomy still remains the surest, safest means not just of controlling thyrotoxicosis but of curing it.

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CHAPTER VI C

RADIOACTIVE ISOTOPES OF IODINE—USE IN THERAPY OF DIFFUSE TOXIC GOITER

THE NATURALLY occurring iodine has an atomic weight of 126.9 and is not radioactive—i.e., its atoms do not spontaneously disintegrate so that beta rays (high speed electrons) are emitted. In 1934, Fermi showed that artificial radioactivity could be induced by neutron bombardment. Since then, 9 radioactive isotopes of iodine have been discovered. Because artificially radioactive elements are known to resemble very closely non-radioactive isotopes (of the same element, in each case, of course), it was obvious from the first that radioactive iodine offered a new tool for research and—possibly—a new means of treatment in hyperthyroidism at least, if not in certain forms of thyroid carcinoma. The physiological activity of the various isotopes of the same element does not differ from isotope to isotope—except as regards the physiological effects of the high speed electrons emitted in the case of radioactive isotopes. Artificially produced radioactive iodine enters into the same biochemical reactions and physiological roles as does the non-radioactive naturally occurring iodine. Consequently, the metabolism of iodine within the thyroid and other tissues of the body can be traced readily by the addition of small amounts of radioactive isotopes to iodine administered in a tracer dose—which contains tagged or labeled atoms, the tagging or labeling being the result of the radiations of the disintegrating atoms. The distribution of radioactive iodine throughout the various tissues can be determined by use of the Geiger-Müller counter which detects the radiations produced by the exploding atoms.

The radioactivity of a single dose of labeled iodine permits us to follow the metabolic rate of iodine and to differentiate between the newly administered atoms and those already present within the thyroid or other tissues of the body. Indeed a mere trace of radioactive iodine within a given quantity of iodide serves to label the entire dose, the ratio of tagged atoms to non-radioactive atoms remaining the same.

for varying periods after administration, the period depends upon the rate at which the radioactive isotope disintegrates. The radioactive isotopes which have been the most extensively used are 131 (half period, 8 days) and 130 (half period, 12.6 hours), although in the first studies an isotope with a half life of only 26 minutes was used, being the only form available to certain workers.

Numerous researches have already established the unique value of radioactive iodine in studies on the metabolism of iodine not only in experimental animals but also in normal individuals, in patients with thyroid disorders, and certain types of cancer of the thyroid. Further, promising results have been obtained by therapy with radioactive iodine in certain hyperthyroid patients especially those with diffuse toxic goiter.

Tremendous quantities of radioactive iodine are produced as a byproduct in nuclear chain reacting piles, but most of the radioiodine used in tracer studies and therapy has been produced by the nuclear bombardment of metallic tellurium as the target for high speed deuterons (14 million electron volts) in the cyclotron.

In the first recorded studies of thyroid physiology with radioactive iodine as an indicator, Hertz, Roberts, and Evans (1938) irradiated ethyl iodide with radium to obtain radioiodine, which they injected intravenously into rabbits. The half period of the radioactive isotope which these investigators used was only 26 minutes, hence accurate measurements could not be extended beyond 40 minutes. The individual disintegrations of the radioactive atoms were recorded by means of a Geiger Muller counter and a standard vacuum tube amplifier, the radioiodine in the various tissues being thus detected. The rapidity with which the thyroid accumulates iodine is remarkable. Hertz and co-workers found significant accumulation of injected radioactive iodine within a few minutes after administration of the tracer dose. Negative results were obtained with radio-active bromine, this shows the specificity of action of the thyroid in its accumulation of iodine. It was also observed that hyperplastic thyroid glands, within the same period of time, collect several times as much radioactive iodine as normal glands of control rabbits. No toxic reactions were noted in any of the 48 rabbits which were given radioactive iodine intravenously. In later experiments, Hertz et al (1939) reported that the collection of radioactive iodine by the thyroid parallels the increases

in basal metabolic rate, the mean acinar cell height, and the weight of the thyroid gland that result from the injection of thyrotropic hormone

Hamilton and Soley (1939), studying patients with hyperthyroidism, confirmed the findings of Hertz and his associates with respect to markedly increased iodine uptake by hyperplastic glands. Hamilton and Soley administered to each patient a tracer dose consisting of a total of 14 mg of iodine in the form of sodium iodide in distilled water and providing between 24 and 100 microcuries of radioactive iodine. The radioactive iodine had been prepared by neutron bombardment of a tellurium target placed in the cyclotron at the University of California. Normal human controls as well as patients with various types of goiter were studied after oral administration of the labeled iodine. None of the patients had received iodine before the tagged element was given and no additional iodine was administered until the experiments were concluded. The observations of Hertz et al on rabbits were fully substantiated not only with respect to the increased uptake of hyperfunctioning glands but also as concerned the time for initial thyroid collection — which appeared to be simply the time required for the iodine to reach the thyroid. Iodine was shown to be stored to a significant extent only in thyroid tissue, although a certain percentage of the dose is always distributed to all the tissues. The activity of the diffusely distributed iodine is invariably so slight as to escape detection. The tagged atoms are excreted gradually via the kidneys. Hamilton and Soley failed to observe more than a few per cent in the feces. The prompt accumulation of radioactive iodine by the glands of patients with hyperthyroidism was followed by a rapid loss of from 50 to 80 per cent of the labeled atoms which had been taken up during the first few hours subsequent to the administration of the tracer dose. Hamilton (1942) points out that these results prove hyperactive thyroid cells to have an altered mechanism for the retention of recently deposited iodine, thus, their marked avidity for the accumulation of iodine is offset by the rapid loss. Patients with hypothyroidism show a reduced capacity to concentrate iodine in their thyroids. This small uptake of iodine by the glands of hypothyroid patients may be explained, according to Hamilton (1942), by the fact that their thyroid tissue cannot produce thyroid hormone in sufficient quantities to meet metabolic requirements. Evidence was obtained in

favor of the view that the main factor in the failure of the thyroid of such patients to accumulate iodine is the inability to synthesize the thyroid hormone

In a later series of experiments, Hamilton and his associates, large doses of radioactive iodine (I^{131} with a half life of 8 days) were given to rabbits and dogs. These large doses caused almost complete destruction of the thyroid gland in every animal. There was no evidence of damage to the other tissues of the body. Subsequently, much smaller doses of radioactive iodine were given orally to 3 patients with hyperthyroidism. Each of these patients showed marked clinical improvement within 4 to 6 weeks, the basal metabolic rate ultimately approached normal levels. Hamilton and co-workers were not able to observe any untoward reactions attributable to the radioactive element, either during or after the period of administration of the new therapeutic agent. After $4\frac{1}{2}$ months, 2 of the patients were in a state of complete clinical remission, the third patient required only 1 more (small) dose of radioactive iodine.

These early reports of favorable results with radio iodine in hyperthyroidism at once attracted attention throughout the world and have stimulated extensive research wherever radioactive iodine has been available. Thus far, however, most of the investigations have been on animals and have involved fundamental physiological and biochemical considerations. The number of recorded cases of clinical applications is steadily increasing, the early results are definitely impressive.

BIOCHEMICAL INVESTIGATIONS

Tracing Effects of Sulfonamides Hypertrophy and hyperplasia of the thyroid gland result from the administration of any one of a number of sulfonamides, just as in the case of thiourea and thiouracil (Astwood, 1943, MacKenzie, 1943). These compounds appear to diminish the production of the thyroid hormone, Astwood has suggested that their action is elsewhere than in the gland and may be concerned with the synthesis of some essential component or precursor of the hormone. As Franklin and Chaikoff (1943, 1944) point out the sulfonamides could interfere with the following reactions (1) selective removal of the circulating inorganic iodine by the thyroid, (2) incorporation of inorganic iodide into thyroxine and diiodo tyrosine, and (3) release of the hormone into the blood. Morton and

Chaikoff (1943), using labeled iodine, showed that surviving preparations of thyroid tissue (rat dog sheep) readily convert inorganic iodide to thyroxin and diiodotyrosine. Subsequently, Franklin and Chaikoff (1944) demonstrated that the conversion of inorganic iodide to thyroxin and diiodotyrosine is directly interfered with by the sulfonamides, the incorporation of radioactive iodine into thyroxin and diiodotyrosine by surviving slices of thyroid tissue was measured and it was found that sulfanilamide, sulfapyridine, sulfaguanidine, and sulfathiazole inhibit the formation of radiothyroxine and radiodiiodotyrosine. Nevertheless, the capacity of surviving thyroid slices to remove radioactive iodine from the Ringer's solution—that is the extraordinary iodine-concentrating capacity of thyroid tissue—was not appreciably reduced by the presence of a sulfonamide. The precise mechanism by which the sulfonamides inhibit formation of thyroxine and diiodotyrosine remains undetermined.

Tracing Effects of Goitrogenic Substances Biochemical investigations of the goitrogenic effects of thiourea, thiourea derivatives (such as allylthiourea and phenylthiourea), cyanides, thiocyanate and the sulfonamides have been facilitated by utilization of radio iodine (especially ^{131}I). In common with most authors we regard it as established that the hypertrophy and hyperplasia of the thyroid gland induced by these substances are not results of the direct stimulation of thyroid tissue—their goitrogenic effects are not observed in the hypophysectomized animal and increased thyrotropic hormone activity appears to be the cause of enlargement of the glands (see page 151). Using labeled iodine, Franklin, Chaikoff and Lerner (1944) recorded excellent evidence in favor of the view that thiourea, thiouracil and allylthiourea in exceedingly minute concentrations inhibit the conversion of circumambient inorganic iodide to thyroxin and diiodotyrosine by surviving thyroid tissue. The reaction involved is extremely sensitive—allylthiourea in a concentration as low as 10^{-4}M markedly diminishes the formation of radiothyroxine and radiodiiodotyrosine. Further p-aminobenzoic acid and p-aminophenylacetic acid also were found to have a markedly inhibitory influence on the rate of conversion of inorganic iodine to thyroxin and diiodotyrosine. These 2 compounds not only have goitrogenic properties but also structurally resemble the sulfonamides.

The administration of thiouracil to experimental animals is fol-

lowed by the development of hyperplastic, hypofunctioning thyroid glands, this effect has been attributed (by most workers) to an increased secretion of thyrotropic hormone by the pituitary gland. Further, injection of thyrotropic hormone leads to the development of a hyperfunctioning, hyperplastic goiter. Larson et al (1945a) have compared the effects of thiouracil and of injected thyrotropic hormone on the concentration of radioactive iodine and the anatomic changes induced in the thyroid, and have thus been able to investigate directly the physiologic differences between these two goitrogenic agents. During the first 5 days after the administration of thiouracil to the chick, no anatomic changes were detectable. Subsequently, however, hypertrophy and hyperplasia—as measured by increase in thyroid weight and mean acinar cell height—rapidly developed. Except for this lag in onset, however, the histologic changes resulting from thiouracil administration were observed to be identical with those resulting from injection of thyrotropic hormone. Thyroids made goitrous by administration of thiouracil were found to have a greatly reduced capacity to concentrate (radioactive) iodine, following the withdrawal of thiouracil, at least some thyroids were observed to acquire rapidly a capacity to store iodine in much larger quantities than could the control glands—collection of iodine being increased to about the same value as in the case of thyroids rendered hyperplastic by injection of thyrotropic hormone. These authors believe that the capacity of thiouracil to diminish the collection of radio iodine by the thyroid may be its essential and primary effect. The thyroid hyperplasia which develops later appears to be functionally as well as histologically identical with that induced by thyrotropic hormone injection.

The extensive studies of Harington indicate the probable course of events in the synthesis of thyroxine by the thyroid gland, diiodotyrosine seems to be the natural precursor of thyroxin. The natural synthesis of the latter may be assumed to involve two chief steps: (1) iodization of tyrosine and (2) the union or coupling of two diiodotyrosine molecules to form thyroxin. Free iodine must be present for the first step to be accomplished. But iodine is taken up in the form of iodid by the thyroid—consequently, for free iodine to be produced and diiodotyrosine to be synthesized, a strong oxidizing agent is required. Larson et al (1945) have remarked that thiouracil and substances having a similar physiological action may act primarily

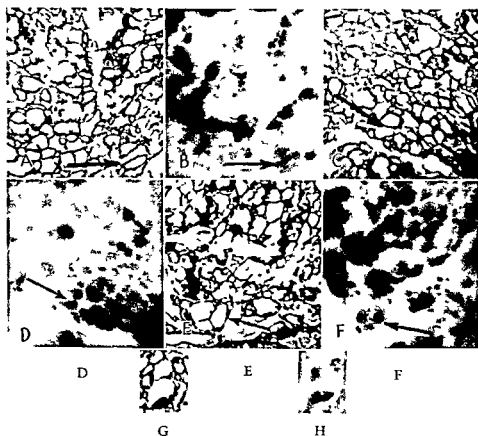


Fig. 22 Sections of the thyroid gland of a patient (R.D.) with exophthalmic goiter and a basal metabolic rate of plus forty per cent and the corresponding radioiodine autographs. A comparison of the photomicrographs (A and C) which are typical of toxic diffuse hyperplastic goiter and the radioautographs of these sections (B and D) again emphasizes that the radioiodine is deposited in the colloid. This is especially clear when comparing the arrow indicated areas. (From Leblond C. P., Fertman M., Been Puppel I. D., Curtis George M. Radioiodine Autography in Studies of Human Goitrous Thyroid Glands. *Archives of Pathology* 41: 510-515, 1946.)

A

B

C



D

E

F

G

H

Fig. 23 Sections of thyroid gland of a patient (ES) with non toxic diffuse colloid goiter and a basal metabolic rate of minus seven per cent and the corresponding radio iodine autographs. A comparison of the photomicrographs (A, C, E, and G) and the radioautographs of these sections (B, D, F, and H) demonstrates that the radio iodine is deposited in the colloid. This remarkable feature is re emphasized when the arrow indicated follicles of A, C, and E are compared with the arrow indicated radioautographic areas of B, D, and F. Note that the radioautographic areas are almost similar in configuration to the colloid areas present. Note also that the vacuole in section G shows practically no radioactivity in H. (From Leblond C. P., Fertman M. Been Puppel, I. D. Curtis, George M. Radio iodine Autography in Studies of Human Goitrous Thyroid Glands, *Archives of Pathology* 41: 510-515, 1946.)

by inhibiting the enzyme system which provides the oxidizing agent necessary for the synthesis of thyroxin. Another suggestion made by these authors is that thiouracil may have some obscure effect on iodides so that they are prevented from entering into the indicated organic synthesis, this effect may take place through biochemical processes induced to occur in thyroid tissue. Larson and his associates observed inhibition of the capacity of the thyroid to collect iodine following the injection of thiouracil, this inhibition attaining a maximum within an hour after the initial dose of thiouracil. Further, these workers have demonstrated that thiouracil likewise inhibits collection of radio-iodine by (1) the thyroid of the normal animal, (2) the thyroid made hyperplastic by injection of thiouracil, and (3) the thyroid made hyperplastic by injection of thyrotropic hormone. This effect disappears within 24 hours. Larson et al. conclude that the inhibitory influence of thiouracil on radio iodine collection by the thyroid may be the result of suppression of synthesis of iodine containing compounds of the gland. These studies tend to confirm the findings of Astwood (1913), which indicate that thiouracil acts primarily by inhibiting thyroid hormone production, thyroid hyperplasia being a secondary result.

Taurog, Chaikoff, and Franklin (1945) tested 40 compounds structurally related to the sulfonamides and aminobenzoic acid for their effects on the *in vitro* conversion of ^{131}I (radioactive iodine) to thyroxin and diiodotyrosine by surviving thyroid slices. They found that a free aromatic group or a free hydroxyl group increases inhibitory activity in the conversion of inorganic iodide to thyroxin and diiodotyrosine by thyroid tissue. Acetylation, causing blocking of the amino group also increases inhibitory activity. Such groups as the sulfonamide sulfonic acid and carboxyl were shown to be unrelated to activity in the interference with conversion of iodide to thyroxin and diiodotyrosine. These authors believe that ease of oxidizability is definitely correlated with inhibitory activity among the compounds tested.

Extending the line of investigation instituted by Leblond and Sue (1910), who had demonstrated the increased capacity of the thyroid to fix radioactive iodine following injection of thyrotropic hormone, Keating et al. (1945) studied the effects of this hormone on the histologic structure of the chick thyroid, which is remarkably sensitive to such stimulation. Keating and his associates observed that changes

in the weight of the thyroid or its size may be the result of changes in (1) vascularity, (2) stroma, (3) colloid, (4) size of acinar cells, or (5) number of acinar cells. Injection of thyrotropic hormone suggested that several of these factors are caused to undergo change. A definite increase in the size of the acinar cells was noted, together with an increase in blood supply — but at the same time there was a decrease in the quantity of colloid material. These workers expected that they would find an early and pronounced increase in the quantity of stored (radioactive) iodine as a result of thyrotropic hormone stimulation, many experiments, however, failed to reveal any changes in this function until after histologic changes become marked. With increased thyrotropic stimulation, the increase in the capacity of the thyroid to collect radio iodine does not appear to keep pace with the increasing weight of the gland. When varying degrees of stimulation were produced by these investigators it was ascertained that after injection of small amounts of thyrotropic hormone, increases in the storage of radio-iodine exceed the anatomic changes. But when larger quantities of thyrotropic hormone were given the storage of iodine did not increase in proportion. From these observations it may be concluded that the extensively growing and proliferating thyroid has for a time at least a lessened capacity for iodine storage.

In the same studies, it was found that after the injection of thyrotropic hormone, thyroid hyperactivity is speedily detectable, and becomes conspicuous within twenty four hours, as shown by the increase in the mean acinar cell height. No increase in the stored radioactive iodine was detectable until 48 hours had elapsed. Loss of iodine previously stored in the thyroid was promptly accelerated by administration of the thyrotropic hormone, this may be assumed to indicate an accelerated secretion of thyroid hormone from the gland as a result of stimulation by thyrotropic hormone.

A number of workers have shown that, soon after injection of radioactive iodine, the uptake of the labeled substance is greater in the case of the stimulated thyroid and smaller in the case of resting thyroids, as compared with uptakes in controls (Hertz and co workers, 1938, 1940, Leblond and co-workers, 1940, 1941, 1944, Hamilton and Soley, 1940, 1942, Horton et al 1941, 1942). Using the autograph method, Leblond (1944) essentially confirmed earlier determinations made with radioactive iodine and resting as well as stimulated thyroids.

He points out, further, that the radioactive iodine is more abundant in the acidophilic than in the basophilic colloid, whatever the condition of the thyroid, stimulated or resting. This investigator has noted that the presence of more radioactive iodine in the acidophilic follicles may be explained in either of two ways: (1) these follicles take up more radioactive iodine, or (2) acidophilic follicles release less radioactive iodine. The acidophilic follicles are known to be characteristic of the inactive gland and fix little iodine, hence it does seem likely that acidophilic follicles actually incorporate 131 more actively than do the basophilic follicles. It is significant that acidophilic follicles found in exceptional instances in the stimulated thyroid have a low epithelium and small nuclei which cause them at least to appear less active than the basophilic follicles within the same gland. This is additional evidence against the view that acidophilic follicles are more efficient in extracting iodine from the blood. It must be concluded that the basophilic follicles are featured by a more rapid turnover and excretion of iodine than are the acidophilic ones which must retain the fixed iodine longer. In fact, Morton et al. (1941) have shown that organic iodine is excreted from the thyroid more actively when the gland is stimulated and therefore presumably basophilic. Presumably acidophilic glands from hypophysectomized animals show, in contrast, a markedly diminished rate of excretion of radioactive iodine (Morton 1942).

Leblond (1944) thinks that the staining affinity of the follicles as related to the excretion of the iodized products may be explained by De Robertis' findings: a larger quantity of proteolytic enzyme is present in the colloid of stimulated (and therefore presumably basophilic) glands than in the colloid of normal glands. The hydrolysis of the colloid, a process believed to precede the diffusion of iodized products from the gland, may be facilitated by these enzymes (Lerman 1942). Basophilic follicles may more rapidly eliminate radioactive iodine because of a more rapid hydrolysis of the iodine-containing substances of the colloid. Whereas the entry of iodine into thyroid tissue seems to be directly dependent on the size and activity of the acinar cells, the elimination of the iodized products appears to be intimately related to the condition of the colloid (Leblond, 1944). The uptake and release of iodine may proceed at different rates in different follicles of the same gland, but it must be assumed that both processes are con-

tinuously under way in all follicles, even those of the comparatively inactive glands of hypophysectomized animals

Metabolism of Radio-Iodine as Affected by High and Low Temperatures. Authorities are in general agreement that the activity of the thyroid is increased by exposure to cold and is decreased by exposure to elevated temperatures. Leblond et al (1944) used radioactive iodine (132) to determine the activity of the thyroids of rats exposed to extremes of temperature. The thyroid tissue of animals exposed to cold (4°C) for periods varying between 1 and 26 days fixed (or concentrated) much more radioactive iodine than did the controls. Exposure to cold for 1 day resulted in the fixation of 1.85 times as much iodine as was bound by the thyroid tissue of controls. Exposure to cold for 26 days led to the fixation of 2.7 times as much radio iodine as in the instance of control animals. In distant contrast are the results of exposure of the animals to heat (32° to 34°C), much less iodine being incorporated by the thyroid tissue of these animals. Animals exposed to elevated temperatures for 7 days fixed only 0.69 of the amount concentrated by the controls. Those exposed to high temperature for 29 days fixed still less — 0.55 the control value. Histological study provided evidence that the cellular changes paralleled the increase or decrease in thyroid activity as shown by the analyses subsequent to administration of the labeled iodine. Further, in the instances of the animals exposed to cold, separation of the iodine fractions of the thyroid at various time intervals demonstrated that the turnover of thyroxin and the excretion of iodized products are increased to approximately twice the normal rate. Taking into consideration iodine fixation, thyroxin turnover and excretion of iodized products, the effect of heat is less marked — but, although slight, the influence of heat can be observed as early as one day after the beginning of the exposure and persists for some 26 days.

IODINE METABOLISM IN GRAVES' DISEASE

In the first extensive studies with radioactive iodine in Graves disease, Hertz, Roberts and Salter (1942) administered the labeled element (chiefly the 8 day isotope, 131) to patients with this thyroid disorder and to normal controls. These workers were able to follow the absorption and excretion of the radio-iodine in doses of various sizes, administered at various times during the course of preoperative iodini-

zation The patients who were studied had had no iodine previous to hospital admission In 19 cases, glands were obtained at operation but it was found that the uptake of the tagged element by the thyroid could not be directly determined from tissue samples, the radio iodine having non uniform distribution through the gland tissue Hence relative measurements of the concentration of labeled iodine in the thyroid were made by use of a Geiger Muller counter After a preliminary period of bed rest, the basal metabolic rate was determined and afterwards the tracer dose was orally administered When external measurements indicated that the thyroid iodine level had reached a relatively constant value, routine iodination was instituted Following the development of maximal clinical as well as metabolic response (within a week or 10 days), subtotal thyroidectomy was performed on the 19 patients an estimate of the residual thyroid tissue being made in each instance Histologic study was made of a portion of the excised tissue, chemical fractionation of the remainder being carried out The fractionation was to determine the concentrations of the thyroxin like and diiodotyrosine like substances Analyses of blood and urine were also performed Three cases were not operated on for clinical reasons

A comparison was made of the patients who received iodine before the administration of radio-iodine and patients given similar doses of the tracer substance About 20 per cent of a 2.5 mg. labeled dose was collected and concentrated in the thyroid of the typical, completely iodinated patient, the elapsed period being about 24 hours A patient who has been less completely iodinated may be expected to show a much greater collection of labeled iodine from a comparable dose A previously uniodinated patient will, according to Hertz and co workers exhibit almost complete collection the hyperplastic gland of Graves disease may collect initially 80 per cent or more from a sufficiently small dose (2 mg.) These results are quite in accordance with those obtained by Hamilton (1942) The larger the dose of labeled iodine, the smaller the percentage collected by the thyroid gland The large percentage uptake from a small dose in Graves disease (patient not previously iodinated) is even greater than one would expect in view of the observations on animals whose glands have been rendered hyperplastic by the administration of thyrotropic extract of the hypophysis

It is noteworthy that much of the iodine from larger doses ap-

parently becomes diffusely distributed throughout all the tissues of the body. In most subjects, the initial iodine collection by the thyroid does not exceed about 5 mg from a single dose. Thus, there is a dosage "ceiling" above which the average collection by the thyroid remains constant, a very low percentage uptake being characteristic especially in the case of the iodinated patient.

Iodine Loss (Excretion) In normal individuals, very little iodine is excreted within the first 4 or 5 days subsequent to the administration of a dose of the tracer substance. On the other hand, as noted also by Hamilton (1939, 1942), the untreated cases of Graves' disease show a marked loss of iodine both from the gland and by excretion via the kidneys during the same period, these are the subjects which manifest maximal uptake of (tracer) iodine. Hertz, Roberts, and Salter remark that the tendency of thyroid tissue in Graves' disease is not to become saturated with iodine by accumulating small quantities but is rather to take up this iodine and secrete it — possibly in calorigenic form as hormone (or modified hormone).

Urine studies showed that about half of the tracer iodine, initially stored by the thyroid but soon secreted or released, may not appear in the urine of the patient with Graves' disease. Only a very small percentage of iodine is excreted by way of the feces (Hamilton and Soley, 1939). Attempts to detect the location of this iodine by means of the Geiger Muller counter have not been successful. This lost iodine must be more or less uniformly distributed throughout the body tissues. Hertz, Roberts and Salter have considered the problem as to whether this iodine is in organic or inorganic combination, above all, is it in calorigenic form? Analysis of the radioactive material in the blood provided evidence that the greater part of the labeled iodine is in protein combination and therefore may be calorigenic form.

Analysis of Thyroid Tissue after Operation. Analysis of thyroid tissue after operation on patients who had received tracer doses of iodine revealed that the general trend is for the tracer atoms to be increased in the thyroxine like fraction and decreased in the non thyroxine like fraction as the time following administration increases.

These early studies obviously have important bearing on the problem of the therapeutic use of radioactive iodine in Graves' disease, as discussed in a later section (page 186).

RADIO IODINE IN CHILDHOOD HYPOTHYROIDISM

The well known fact that the extremes of thyroid dysfunction — as represented by the myxedematous gland and the hyperplastic thyroid in toxic goiter — show certain similarities, still inexplicable, has been once again demonstrated, in radioactive iodine studies in childhood hypothyroidism reported by Hamilton Soley, Reilly, and Eichorn (1943). The uptake curves of radio iodine in two goitrous patients were found to resemble closely the corresponding curves obtained in patients with toxic goiter by Hamilton (1942) and others (Hertz and Roberts, 1942a, b).

Less than one fiftieth the amount of radioactive iodine necessary to produce (observable) biological changes was administered by Hamilton et al (1943) to 10 children with severe hypothyroidism, 3 children were less than 1 year old, the ages of the other 7 ranging from $3\frac{1}{2}$ to 19 years (The 19 year-old adolescent was a typical cretin). None received iodine for 6 weeks prior to the giving of the tracer dose, during a period of several hours prior to the test, no food was permitted. Each of the 2 youngest children was given 3.5 mg of sodium iodide containing a known percentage of radio-iodine, and each of the 8 other patients received 11 mg of the same preparation. Uptake was measured by a Geiger Muller counter placed over the isthmus of the thyroid gland. The two patients, aged $4\frac{1}{2}$ years and 19 years respectively, who had goiters, showed rapid and complete uptake of the labeled iodine within 4 hours, but also a rapid loss of about three fifths of the accumulated iodine within 24 hours, a more gradual loss being observed during the next 4 days. Hamilton et al, however, did not determine the form in which the tagged iodine was lost from the thyroid, but they state that, if the iodine were in the form of active hormone, then such cases should be able to maintain themselves in a normal state of thyroid function when iodine is administered in sufficient quantity. Nevertheless, we would like to stress the point that there must be many exceptions to such a generality. It is well known that many goitrous patients with severe hypothyroidism are not benefited by iodine alone — by any means.

It is noteworthy that 8 other patients showed inability to absorb and concentrate within the thyroid gland enough iodine to maintain normal iodine balance. Their thyroid tissue accumulated so little iodine

that accurate measurements were not possible until 5 days had elapsed. Meanwhile, most of the labeled element was excreted, excepting a minor fraction stored within the gland. Two cases were found to have accumulated 0.05 per cent or less of the radio iodine, 2 accumulated 0.1 per cent, and 3, 0.5 per cent or slightly more, within the gland tissue. In earlier studies, it has been observed that normal children (ranging in age from 4 to 10 years) may be expected to retain some 2 per cent of the radioactive element, the normal adult gland retains approximately twice as much, after the elapse of 5 days. Palpable glands were present in the 3 children whose uptake was 0.5 per cent or slightly more.

When in a later study, each patient was given a much smaller dose of radio iodine (0.1 microgram), the uptake was relatively much greater in 4 patients with hypothyroidism but without goiters, by the end of the fifth day after ingestion of the tracer iodine, these patients accumulated from 1.9 to 4.5 per cent of the radioactive atoms within their thyroid glands. These determinations are in accord with the findings repeatedly made in adults: thyroid tissue will accumulate a greater proportion of a small dose than of a large dose of labeled iodine (Hertz, 1941, Hertz and Roberts, 1946). Hence, in children as in adults, the administration of very minute amounts of radioactive iodine will serve to reveal active thyroid tissue (capable of concentrating iodine) in hypothyroidism or myxedema. In normal adults a dose of approximately 2 ten millionths of a gram of tracer iodine may be expected to result in a 20 per cent uptake or from 4.5 to 10 times the uptake noted when the test dose is 14 mg of radioactive preparation. In the 4½ year old goitrous patient (who had a thyroid gland weighing an estimated 50 Gm) the maximum uptake was approximately 53 per cent, whereas the thyroid of the goitrous cretin aged 19 years (slightly enlarged thyroid) was found to have a maximum uptake of about 33 per cent of the labeled iodine. These two goitrous subjects—as demonstrated by radioautographs of the excised gland—had most of the radioactive iodine concentrated in the cells of the acini rather than in the colloid. Hamilton et al. state: One must assume that some fault prevents release of an active thyroid hormone from the accumulated iodine; otherwise these patients should not have had the severe degree of hypothyroidism which was obvious even on casual clinical examination. In the two goiters (removed within

48 hours after the administration of the tagged iodine), one fifth of the iodine was analytically demonstrated to be in the form of thyroxin, if this thyroxin was not retained by the gland as a result of some obscure pathologic functioning, then these patients presumably would have maintained themselves in normal thyroid balance, according to the authors. It must be observed that these results are only to be expected the thyroid tissue of adults with myxedema are generally non functional, being atrophied and fibrosed.

THYROID CARCINOMA WITH METASTASIS

In cases of carcinoma of the thyroid studied by giving radioactive iodine before operation the malignant tissue removed showed only one hundredth of the quantity of labeled iodine found in the normal tissue of the same gland (Hamilton, Soley, and Eichorn 1940). Commenting on this inability of the carcinoma of the thyroid to concentrate iodine, Hamilton (1942) has remarked that radioactive iodine would not seem to be of therapeutic value in cases of this nature. Frantz and associates (1941), however, note that the types of carcinoma to which Hamilton refers did not appear to be well differentiated, but agree that, except for the adenoma malignum type, chemical analyses reveal low iodine content in carcinomatous thyroid tissue.

We believe that radioactive isotopes of iodine must be assumed to be of insignificant value in all but a very few carcinomas of the thyroid, element 85, or *eka iodine* (page 194) may eventually be found to have somewhat greater effectiveness because of its far more powerful alpha rays. Only in those cases of carcinoma with or without metastases but with *hyperthyroidism* (indicating an excess of functional tissue or hyperfunctioning tissue) would radioactive iodine be expected to have beneficial effects. Well differentiated tumors of the thyroid are very rare. Ward (1944), in an extensive review of surgical material, emphasized the lack of demonstrable correlation between carcinoma of the thyroid and clinical hyperthyroidism, among 168 cases of cancer of the thyroid he was able to find only 1 case of carcinoma in a diffuse toxic goiter. We cannot expect thyroid like functioning in the highly malignant anaplastic carcinomas that grow with extreme rapidity and, having no organoid arrangement, produce no colloid. The histology of the small group of tumors midway between the quite undifferentiated and the well differentiated forms does not suggest

significant endocrine functioning Frantz et al believe that there may be considerable functional tissue in the more benign forms often grouped under the misleading heading of *adenoma malignum*, and observed to be of two main types (1) the papillary form, frequently containing colloid, and comprising a large percentage of the tumors that involve lateral aberrant thyroid tissue — these metastasize usually to lymph nodes and later to the lungs but rarely to the bones, (2) the type which resembles embryonal, fetal or simple adenoma and which exhibits a high degree of differentiation even in metastases — these often undergo widespread metastasis to osseous structures Tracer doses of iodine may be valuable diagnostically, but only in those instances in which localization occurs In several cases, Frantz and her co workers observed that failure of uptake by cancerous tissue does not mean the tumor is not of thyroid origin In 2 cases of colloid containing bony metastases there was no uptake of radioactive iodine A so-called Hurthle cell tumor, presumably functionless was found in one case These investigators were, however, surprised to find no uptake in the other case, in which there was a well differentiated adenoma malignum, the significance of the finding was not clear, especially in view of the determinations made in the following case

In 1 patient, storage of radioactive iodine in a metastasis from a thyroid carcinoma was followed over a prolonged period with remarkable cure by Frantz et al Seven years after an encapsulated, extremely vascular tumor had been removed from the isthmus of the thyroid gland, roentgenograms disclosed metastases (confirmed at autopsy) to the left humerus the lower end of the right femur, the upper end of the left femur and the left parietal bone A needle biopsy of the tumor in the left parietal region and subsequent microscopic examination led to the recognition of a well differentiated adenoma with small colloid follicles Basal metabolic rate and serum cholesterol, however, were within normal limits and remained so Radiotherapy was instituted, but after 2 months it was interrupted to permit the administration of a tracer dose of radioactive iodine (with a half life of 8 days) The Geiger counter showed that the tracer iodine was taken up in considerable quantity by the metastasis in the right femur as well as by the thyroid gland but was not stored to any appreciable extent in the other bony metastases It was considered possible that radiotherapy induced necrosis may account for the lack of

storage in these foci. The rate of disappearance of radio-iodine from the right femoral metastasis paralleled closely the rate of loss from the thyroid gland. The administration of 54 mg of potassium iodide did not wash out the radio-iodine from the gland or this metastasis, hence the authors assumed that the iodine was bound in these foci, probably in organic form as seems quite probable to us. Localization within the thyroid gland and the one metastasis suggested the possibility that a larger dose might afford selective internal irradiation and ten millicuries largely of the 12.6 hour half period isotope, were administered, 6 per cent of the radioactive material was stored in the thyroid and 30 per cent in the right femoral metastasis. A month later a tracer dose was given, the right femoral metastasis showed no uptake this time — a finding interpreted by Frantz et al. as evidence of the effectiveness of the internal irradiation. At least the iodine-storing or fixing capacity of the metastasis in question was impaired. Metastases increased in number and extent, the patient's condition rapidly becoming worse. At autopsy, the final anatomical diagnosis was carcinoma of the thyroid with numerous extensions throughout the body. It is noteworthy that well differentiated tumor tissue found in the metastases had not — except in the instance of the metastases to the right femur — shown iodine storing capacity. Hence it is difficult to agree with Frantz et al. that, in certain cases of this type, effective therapeutic internal radiation of metastases may be achieved with large enough doses of radioactive iodine. In this connection, it must be emphasized that in another case of well differentiated adenoma malignum these workers observed no uptake of radioactive iodine — a finding that should not be surprising in view of the inability of most of the numerous metastases to concentrate iodine, in the case just cited. Frantz et al. mention the case of a child with total thyroidectomy and possible metastatic tumor not demonstrable roentgenologically, the site of persisting disease presumably being located by means of the Geiger counter and radioautographs. We believe that radio-iodine will prove very valuable in aiding diagnosis in this way, but such cases are indeed rare.

The frequency of carcinoma of the thyroid with metastases but without hyperthyroidism is in sharp contrast with the very low incidence of thyroid carcinoma with metastases and hyperthyroidism — functioning ovarian struma not being regarded as of metastatic origin.

but, in all probability, being the result of the growth of embryonically displaced, or ectopic, thyroid tissue. The two unique cases showing the association of adenocarcinoma of the thyroid, functioning metastases widely distributed in the osseous and pulmonary system, and clinical hyperthyroidism have recently (1946) been reported by Leiter and his associates. In this study, radioactive iodine was used as an indicator of the functional activity of the metastases. In one case, tracer iodine showed the absence of functional thyroid tissue in the neck and demonstrated that the metastases were functional and therefore responsible for the hyperthyroidism. The administration of thiouracil effected a complete remission of the hyperthyroid symptoms and signs in both patients within a few weeks, the patients' general condition improved and the plasma cholesterol and blood iodine were brought within the normal range—whereas, previously, iodination had exacerbated the hyperthyroidism. During the period of maximum effect of the thiouracil the urinary excretion of radioactive iodine was doubled. Leiter et al. concluded that thiouracil can suppress hormone production in metastases of adenocarcinoma of the thyroid just as readily as this drug inhibits the same process in the hyperplastic thyroid of ordinary Graves' disease. Withdrawal of thiouracil was followed by prompt recurrence of hyperthyroidism in both patients. One patient died—presumably as a result chiefly of extensive pulmonary metastases, most of which were found to be anaplastic and non functional, as indicated by radio-iodine. Leiter et al. reported that the other patient was being given massive therapeutic doses of radioactive iodine and was still under observation. Nevertheless, if the 2 cases are similar, anaplastic and therefore non functional metastases must be present in the second patient. Consequently, we may doubt the assumption that even massive therapeutic doses would have much effect on the clinical course of the disease, the anaplastic metastases continuing to grow—not concentrating radioactive iodine and therefore being quite unaffected by it, in whatever doses it is administered. It is possible, however, that further investigation which correlates histological data with determinations made by use of both thiouracil and radio iodine will provide information concerning the factors determining whether or not carcinomatous thyroid tissue functions or hyperfunctions, as Leiter and his associates suggest.

Pierson (1944) has reported the use of radioactive iodine as a tracer

substance for differential diagnosis in a case of primary carcinoma of the trachea. This author noted the possibility that the carcinoma in the trachea might be secondary to carcinoma in the thyroid, although roentgenograms revealed no substernal mass suggesting a thyroid gland and size and position of the tumor were quite accurately delineated by laminograms. Following the administration of a small dose of radioactive iodine, Pierson found intense activity (several hundred counts per minute with the Geiger counter) in the lower part of the neck. A second dose, this time 200 microcuries of radioactive iodine, resulted in an immediate increase in general body radioactivity (counts close to the hand, 30 per minute), but the concentration in the neck was not determined. Two days later, several pieces of tumor were removed by use of the bronchoscope and were examined by Dr J G Hamilton. Because no radioactivity was detected in these specimens of the tumor, the presence of normal thyroid tissue within the tumor was ruled out. Nevertheless, metastasis of carcinoma of the thyroid was not necessarily excluded. thyroid carcinoma generally does not collect radioactive iodine after the manner of normal or hyperplastic thyroid, although exceptions have been noted in the instances of well differentiated tumors.

RADIOACTIVE IODINE THERAPY IN HYPERTHYROIDISM

Preliminary Studies The first work with radioactive iodine was done with a view to determining the conditions under which radioactive iodine might safely be administered (1) as a tracer substance in the study of thyroid physiology, and (2) as a new therapeutic agent in certain types of hyperthyroidism. The early studies indicated the methods by which the maximal radiational effect could be obtained in treatment of patients with hyperthyroidism. As Hertz (1911) has pointed out, the only radioactive isotope available in the preliminary investigations (begun in 1937) was I^{124} with a half period of only 26 minutes. It was soon found (Hertz, 1938, Hamilton 1939) that the collection of radio-iodine by the thyroid is very rapid, the quantity present in the gland within 10 minutes after intravenous injection not being exceeded within ninety minutes. When corresponding doses were given, hyperplastic glands were demonstrated to collect more iodine than normal glands. Large doses administered to animals brought about destruction of normal and hyperplastic glands (Hamilton,

1942) Small doses were observed to have no readily detectable injurious effects on normal or hyperthyroid glands. These findings indicated the likelihood of using radioactive iodine on a large scale in the treatment of at least certain types of hyperthyroidism. Hertz and co-workers then began systematic studies of the relations among the dosage administered, labeled iodine, the time of collection, previous iodine therapy, and the functional condition of the thyroid gland. As more strongly radioactive and longer lived isotopes became available, more and more patients with Graves' disease were studied first with tracer doses and later with increasingly large therapeutic doses. The partition of iodine among the various iodine fractions in the thyroid and in the blood was investigated chemically. In 1940, Hertz et al. reported the new technique of multiple labeling which makes possible the tracing of different doses of iodine at the same time. With this new technique it was found that the collection from a second dose of radioactive iodine is almost without exception less than that from the first dose. Therefore it was suspected that the routine pre-operative massive iodination in Graves' disease may be unnecessary. Later work has established that response to protracted iodination is no greater than response to a single dose of iodine (Hertz 1941).

Using an externally placed Geiger Muller counter to measure the relative activity of stored radioactive iodine as a function of time, and making a single (absolute) determination after surgery, Hertz (1941) was able to calculate the absolute content of radio-iodine within the thyroid at any previous time. Thus it was discovered that the initial collection of iodine by the thyroid in previously untreated cases of Graves' disease may be between 80 and 100 per cent when the dosage is small (0.2 to 5.0 mg). In previously iodized patients, in normal controls and in all subjects receiving large doses, the quantity of iodine collected by the thyroid is considerably smaller. Other preliminary work involved observation of radioactive iodine metabolism in isolated thyroids surviving in a perfusion apparatus. Results obtained by such investigations prepared the way for the extensive clinical trial of radio-iodine in Graves' disease (Hertz and Roberts, 1946, Chapman and Evans, 1946).

DOSAGE

In the first studies on hyperthyroid patients, very small doses were used (Hamilton and Lawrence 1942; Hamilton, 1942). Dosages are usually expressed in millicuries, one millicurie being 37,000,000 disintegrations per second. Irradiation by x rays produces its therapeutic effects through the action of secondary highspeed electrons, the x rays themselves, of course, being very short electromagnetic waves similar to the gamma rays of radium. Radioactive isotopes of iodine emit beta rays — high speed electrons, consequently, the action is essentially like that of radio iodine. Radiation doses in the case of radioactive iodine can be expressed in terms of roentgen units, although the beta rays have a short maximum range — only a few millimeters (of tissue). Because of the short range of the high speed electrons from radioiodine, the tissue effects of these beta rays are limited to cells within the immediate vicinity of the (concentrated) radioactive isotope. The dose is proportional to the concentration of the isotope within the thyroid tissue.

As Hertz and Roberts (1946) point out, the probable values of radiation dosage delivered in the thyroid may be calculated as follows. First, the fractional uptake of radioactive iodine by the thyroid has to be estimated. Next, the weight of the patient's thyroid must be estimated (by palpation). Also to be taken into account are the known pattern of uptake and retention of radioactive iodine by the hyperplastic thyroid, and the known energy of the radiations from iodine isotopes 130 and 131 . Hertz and Roberts have suggested the following formula

$$\text{radiation in roentgen units} = \frac{10,000 \text{ (dose of } ^{130} \text{ in millicuries)} \times \text{(fractional uptake of thyroid)}}{\text{Weight of thyroid in grams}}$$

In the instance of 131 , the constant 117,000 replaces the constant 10,000. For example, in the case of 130 , a net collection of one millicurie in a 30 Gm thyroid gland affords a total of about 333.33 roentgens in decaying to zero.

The initial rate of delivery of a 1,000 roentgen dose is approximately 55 roentgens per hour in the instance of 130 , whereas 131 initially delivers only 3.6 roentgens per hour. Hertz and Roberts state that while the total radiations delivered by the two isotopes (130

and 131 , as produced in the cyclotron by deuteron bombardment of tellurium) are comparable, the effectiveness of the long period isotope (131 , with a half period of 8 days) is open to question because of the low rate at which radiation is delivered and because of its release from the thyroid as the days pass. These authors make the assumption that the 130 is the origin of the significant radiation. At best, calculation of radiation dosage by the formula given is far more accurate, errors of 50 per cent or more in the estimate of the radiation (received by the thyroid) are to be expected.

(The minimum biologically effective dosage appears to be within the neighborhood of 1,000 roentgens (130 , 12.6-hour isotope, radiation from the 8 day isotope, 130 , being disregarded).)

Chapman and Evans (1946) observe that the tissue radiation dose may be predicted quantitatively for an average patient by taking into consideration only the number of millicuries of 12 hour iodine to be given per estimated gram of thyroid tissue (as suggested by Hertz and Roberts), but patients manifest decided variations from this estimated tissue radiation dose. The main factor causing these variations is the varying retention among different patients, errors always arise from the assumption of a uniform picture of iodine retention. The estimate of the thyroid weight and the estimate of radioactive iodine uptake by the gland are other sources of error.

Chapman and Evans (1946) point out that the shape of the iodine retention curve (Hertz, Roberts and Salter, 1942) is an essential consideration in reaching a reasonably accurate estimate of the tissue radiation, also the urinary excretion of radio iodine must be measured. They advise that the amount of 8 day radioactive iodine (130) when present, be taken into consideration. Whereas a concentration of 1 millicurie (37,000,000 disintegrations per minute) of 131 (12 hour half period isotope) per gram of thyroid tissue yields 12.3 roentgens per minute, an additional 0.85 roentgen per minute is delivered by every 0.1 millicurie of 130 which may be present (per gram of thyroid tissue). We would also like to emphasize that 90 per cent of the total radiation dose from 131 is delivered within the first 36 hours after the dose is administered, for the first 60 hours, the tissue dose per hour is largely that of the 12 hour isotope. The radiation from 130 subsequently adds about 2 per cent per day to the total radiation from 131 .

RESULTS OBTAINED WITH RADIOACTIVE IODINE (130 AND 131) IN GRAVES DISEASE

Twenty nine cases of hyperthyroidism were treated by Hertz and Roberts (1946) during the period 1941 to 1946. Their patients had no previous iodine treatment and were judged clinically to have hyperthyroidism. These workers administered by mouth sodium iodide containing both the 12.6-hour isotope (130) and the 8 day isotope (131), 90 per cent of the activity at the time of administration was delivered by the 12.6-day isotope. The total activity administered was from 0.7 to 28 millicuries. Divided doses were given in 10 cases; in the other nineteen cases the total dose was administered at one time. To insure maximum concentration of the radioactive isotopes by the thyroid the total quantity of iodide was kept below 2 mg. An indirect estimate of the thyroid retention of radio-iodine was obtained by measuring the urinary excretion during the first 72 hours after each dose was administered. Hertz and Roberts determined that significant quantities of the radioactive dose are to be found only in the specimens taken during the first 3 days following administration. Fecal excretion of radioactive iodine is insignificant. Release of radioactive iodine from the gland was followed by means of an externally placed counter; these measurements were roughly calibrated against actual direct determination on thyroid tissue specimens obtained at operation. At periods varying from 1 day to several weeks after administration of the radioactive iodine, routine iodination was carried out with non-radioactive iodine which was given in the usual dosage of 5 minims of a saturated solution of potassium iodide twice a day. Frequent determinations of basal metabolic rate were carried out, the entire clinical picture was closely followed so as to evaluate carefully the results of treatment.

When an essentially normal basal metabolic rate had been maintained on routine non-radioactive iodine for some weeks or months this iodination was halted, the basal metabolic response was assumed to indicate satisfactory control of the thyrotoxicosis at that time. The criterion of remission of the disease was failure of the basal metabolic rate to rise subsequent to cessation of iodine treatment. In the first cases, the radiation dosage administered was, on the average, low — hence not uniformly effective. But conservatism was obviously neces-

sary, safe levels of radioactive iodine in such therapy had not yet been determined. No side effects were observed within the range of dosages employed, a maximum of 28 millicuries being administered to 1 patient. In 1 case, the total dosage was regarded as subminimal, i.e., below 1,000 roentgens (estimated). Hertz and Roberts believe that the calculated dosages—between 500 and 2,500 roentgens, plus or minus 50 per cent—administered in those cases in which treatment appeared to be successful are in satisfactory agreement with the x ray dosages generally found effective.

Of the 28 patients who were given radioactive iodine at the level of therapeutic intensity, 5 were later subtotally thyroidectomized and all of the 5 subsequently developed myxedema. Hertz and Roberts state that when therapeutic levels of radio-iodine have been administered and subtotal thyroidectomy is afterwards resorted to, hypometabolism or myxedema will probably develop in most cases. In the remaining 23 cases, subtotal thyroidectomy was not performed, 20 of these patients responded satisfactorily to treatment with radioactive iodine and are no longer thyrotoxic. The other 3 patients must be included in the list of failures, nevertheless, reduction in the size of the goiter was noted in each case.

The choice of the dose to be employed in the treatment of hyperthyroidism by administration of radioactive isotopes of iodine seems to be dependent mainly upon clinical estimation of the size of the patient's thyroid. The dosage range, when a single dose only is to be given, is between 5 and 25 millicuries, according to Hertz and Roberts. These authors conclude that radioactive iodine therapy in Graves' disease is somewhat more effective than orthodox x ray therapy, when comparable radiation doses are given in the 2 types of treatment. They point out that the efficacy of x ray therapy is at times limited by undesirable skin reaction. Besides, Hertz and Roberts suggest that 'intraglandular irradiation within the thyroid cells may offer certain advantages over external irradiation.'

The most important clinical considerations appear to be (1) either no previous iodination or cessation of iodination for some weeks before administration of the radio iodine, maximum uptake of the radioactive element is thus ensured, (2) routine iodination, instituted 1 to 3 days after administration of the radioactive iodine, and (3) the patient must be available for a close follow up. We further

agree with Hertz and Roberts that it is unwise to administer therapeutic doses of radio-iodine to patients with large, involutional goiters or to special cases in the ophthalmopathic group of hyperthyroidism. We emphatically do not agree that this new form of therapy will largely replace the surgical approach now currently in vogue.

Another series (of 22 patients) has been recorded by Chapman and Evans (1946), who found that 14 patients responded well to a single dose of radio-iodine, no other form of therapy being given. Toxic reactions were noted in 6 cases (see page 193). Myxedema followed this treatment in four of the 22 patients. Two patients, although somewhat improved following administration of radio-iodine, still suffered (at the most recent follow up) from mild hyperthyroidism. According to these authors, patients sensitive to iodine or thiouracil and patients who do not respond well to other forms of therapy may show satisfactory response to treatment with radioactive iodine. Disagreeing with Hertz and Roberts, Chapman and Evans claim that ordinary iodine is not necessary at any time after treatment with radioactive isotopes of iodine whether the latter are administered in a single dose or in divided doses.

The 4 patients who developed myxedema as a result of treatment with radioactive iodine received, in each case, a dose of approximately 1 millicurie per estimated gram of thyroid tissue. Although this dosage may eventually be shown to be excessive, in other cases administration of radio-iodine at about the same level did not cause hyperthyroidism. In 2 of these 4 cases, there has been a gradual rise in basal metabolic rate to within the lower normal range.

Seven of the 22 patients had been previously operated on for hyperthyroidism and all of this group showed satisfactory response. Roentgen therapy had been administered to three other patients, but the condition of the patient had not been improved in any of these cases, good results were observed following treatment with radioactive iodine.

It is noteworthy that response to radioactive iodine therapy is not infrequently in inverse proportion to the size of the thyroid gland of the thyrotoxic patient, smaller goiters show a more satisfactory response than do larger goiters. The 8 patients who had the largest goiters in the series required 3 separate doses of radioactive iodine, at intervals of several months, before thyrotoxicosis could be controlled.

SIDE EFFECTS AND POSSIBLE DELAYED REACTIONS

In the therapeutic use of any form of radiation, the possibility of untoward side effects—especially those which may be delayed—must be carefully considered. In their report on 29 cases of hyperthyroidism treated with radioactive iodine, Hertz and Roberts (1946) stated that there were no adverse effects, such as fever, nausea or irradiation sickness, no local effects, either in the oral cavity or over the thyroid, and no increase in the degree of thyrotoxicosis subsequent to the radio iodine treatment.

Nevertheless, these authors remark on the unwisdom of treating patients having large goiters, with secondary involutinal changes, at this time by this means, and also note that the treatment of certain cases in the ophthalmopathic group of hyperthyroidism is complicated by special problems. Chapman and Evans (1946) recorded 6 instances of radiation sickness among 22 patients with hyperthyroidism who were treated with large doses of 12 hour iodine. They observed that toxic reactions to large doses of radio iodine are very similar to the reactions characteristic of acute roentgen sickness. Symptoms included nausea, vomiting, malaise, and fever, in some cases, there was a temporary slight increase in gland size. In 4 of the 6 patients having radiation sickness, the doses were 48 millicuries or more. Leukopenia and other late effects were not observed. Thyroid tissue removed 2 years after this form of radiation did not show any malignant changes. Fibrosis of the thyroid was found in two cases by biopsy after treatment. Four of the 22 patients in this series developed myxedema.

Lawrence (1945) has commented: 'Some workers, after a short experience in the therapeutic use of these substances (artificially produced radioactive elements), have become a bit too enthusiastic regarding their value. As far as I am aware, no cures have been accomplished. The immediate dangerous possibilities of any form of irradiation (x rays, gamma rays, radium, artificial radioactivity) are well known to most physicians, but in addition there are possible delayed effects.' It is to be remembered that among radium dial painters cases of aplastic anemia and osteogenic sarcoma developed after many years. Irradiation has been used experimentally to induce delayed neoplastic changes in animals. A recent editorial (1946) points out that the late development of cancer as a result of irradiation with radio-

active iodine, although perhaps unlikely, is certainly within the realm of possibility, and that at present there is no evidence as to the possible harmful effects of excretion of radioactive iodine. Such excretion may concentrate radioactive iodine sufficiently to damage the cells of the kidney. Possible injury to spermatozoa or ova is still another important consideration. We would like to emphasize the point that these possible dangers of treatment with radio-iodine must be kept constantly in mind. In common with other authors (editorial 1946) we believe that, until careful studies of the tissues of the body long after therapy with radio iodine have been made, it will be impossible to predict the extent to which this form of irradiation will be applied in the control of hyperthyroidism.

ELEMENT 85, EKA IODINE

The recently discovered halogen, element 85, or eka iodine has been produced by the bombardment of bismuth with 32 000 000 electron volt alpha particles. It differs from other artificially produced radioactive elements in that it emits alpha particles. Whereas the beta rays from radioactive iodine, I^{131} , have an average energy of approximately 200 000 electron volts, the alpha particles emitted by element 85 have an average energy of 4 000 000 electron volts. Theoretically, element 85 should be closely similar both chemically and physiologically to ordinary iodine and radioactive iodine, in fact, one of the procedures used in the identification of the new element soon after its discovery was its accumulation in the thyroid of animals.

The data available have demonstrated that element 85 and iodine are not only concentrated by thyroid tissue in a similar manner, but also are excreted similarly (Hamilton and Soley, 1940a, and Hamilton, 1942), although the short half life of eka iodine — 7.5 hours — renders it difficult to trace the metabolism of the new halogen for more than 3 days. It is held as firmly in the thyroid gland as is ordinary iodine, and hyperplastic thyroids of guinea pigs show increased capacity to accumulate it. Hamilton administered element 85 to a patient with a non-toxic goiter and followed the uptake in thyroid tissue by measuring the radioactivity *in situ*. He found that the uptake curve was closely similar to those obtained with tracer iodine in this type of thyroid disorder. Approximately 10 per cent of the quantity administered had been accumulated within the thyroid after 24 hours.

Hamilton and Soley have suggested that element 85 may prove to be superior to radioactive iodine as a therapeutic agent in the treatment of human thyroid disorders in which there is an abnormal increase in the functional activity of the gland. There would be important differences, however, between the radiation from element 85 and that from radioactive iodine (^{131}I). The beta rays of radioiodine have a greater range than the alpha rays of eka iodine. In material such as thyroid tissue each alpha particle gives up its energy within a distance of less than 50 microns whereas the beta rays from radioactive iodine dissipate most of their energy in passing through a distance of some 500 microns. Yet the density of the ionization resulting from the action of alpha particles from eka iodine is more than 200 times greater than that resulting from the beta rays of radioiodine. Hence, those thyroid cells accumulating eka iodine in the largest quantities would suffer the effects of most of the radiation, and other cells outside the short range of 50 microns would escape such effects. The beta rays of radioiodine have a much more diffuse action and radiation effects are suffered by cells several hundred microns distant from those cells which concentrate the radioiodine in relatively large quantities. The actual therapeutic significance of such differences can be determined only by further research.

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CHAPTER VII

PATHOLOGY

DIFFUSE NON TOXIC GOITER (SIMPLE COLLOID GOITER)

IN SIMPLE colloid goiter resulting from deficient intake of iodine, compensatory enlargement of the gland and excessive, often enormous, deposition of colloid are observed. This type of goiter is much less frequently seen today than before the prophylactic use of iodine. Its occurrence is most common from prepuberty to late adolescence. The enlargement varies greatly in extent, it may be scarcely apparent or may reach enormous dimensions. The entire gland may be more or less symmetrically enlarged, or the epithelial overgrowth may be restricted to one lobe or the isthmus, at times the only evidence of the presence of a simple colloid goiter is a localized nodule. When present, accessory thyroids may undergo similar changes and increase in size.

Macroscopically, on section, a vesicular and generally soft glistening colloid mass is noted. Histological examination usually reveals



Fig 24A Colloid goiter — anterior view, girl, age eight

Fig 24B Colloid goiter — lateral view, girl, age eight

mainly normal alveoli which are distended with colloid. The follicles are of various sizes and are lined with flattened cuboidal epithelium. The colloid stains only faintly with eosin — i.e., it is thin and acidophilic. Vacuolization may be encountered along the periphery of the colloid but, as a rule, the acinus is quite filled if not enormously distended by the secretion. Compression and obliteration of the interacinar blood vessels often result from the excessive distention of the acini. Subsequent anoxemia of the cells and cystic degeneration occur in many cases. Fusion of adjoining spaces gives rise to cysts of all sizes. Other degenerative changes include hemorrhage, pigmentation, fatty degeneration, and eventual fibrosis and calcification, there may also be prominent amyloid deposits in the stroma and blood vessels.

Such goiters commonly show formation of new alveoli in foci beneath the capsule and in the stroma, alveoli may also develop anew in hemorrhagic areas. The colloid may be secreted in such abundance that the stroma is infiltrated, the secretion collecting in tissue spaces and lymph channels.

In late stages, the typical picture of functional hyperplasia, colloid retention, minor regenerative growth of alveoli, and lesser inflammatory reaction may be succeeded by profounder pathological developments. Papillary adenomas may grow out into cysts, low grade interacinous adenomas may be produced, and even malignant neoplasms may occasionally take rise. The overgrowth of epithelium and new formation of alveoli characterize the development of interacinous adenomas and may proceed to such an extent that clear distinction between these pathological changes and the changes observed in low grade neoplasms may be lost.

In general, however, simple colloid goiter maintains its distinguishing features without much change for years. And so, in most instances, from the clinical standpoint, the enlargement of the gland may be of only cosmetic importance, but pressure symptoms may develop — especially in cases of intrathoracic goiter, and surgical interference, will be indicated.

DIFFUSE TOXIC GOITER

In hyperthyroidism, the thyroid gland shows varying degrees of enlargement and although we can frequently note a rough parallelism between intensity of symptoms and increase in size of the gland, a

marked enlargement may be associated with only minor symptoms or an extreme thyrotoxicosis may accompany only a minor increase in glandular size. Further, there are notable differences between the histological pictures in different cases of Graves' disease. The acini may be greatly increased in size, with a metaplasia of their lining epithelium so that the usual low cuboidal cells have undergone transition to the high columnar type. Marked epithelial overgrowth produces marked papillary infolding, the folds may nearly fill the lumen of the acinus. At the same time, the amount of colloid is diminished and in severe cases may disappear. When colloid is present, it is vacuolated and stains faintly. Such pathological changes are most frequently encountered in the exophthalmic type of hyperthyroidism.

In other cases, the number of the acini may be greatly increased but the acini remain small. The lining epithelium is cuboidal, the cells are much larger than the normal type of cell, and they may be found to stain intensely with eosin, i.e., are decidedly acidophilic. Here again the colloid is diminished or almost entirely absent. This variety of hyperplasia is but rarely associated with the exophthalmic



Fig. 25. Acute toxic goiter without eye signs. The entire field is made up of newly formed acini. The sparse colloid is granular or palely staining and retracted. The solid cell masses are made up of small nuclei and indefinitely outlined protoplasm, indicating that the proliferating capacity is dominant. (From Hertzler, A. E. *Surgical Pathology of the Thyroid Gland*, Philadelphia, 1936, J. B. Lippincott Co.)

type of goiter, it is frequently observed in severe primary hyperthyroidism which is featured by unusually high basal metabolic rates. It must be remembered however, that papillary hyperplasia and follicular hyperplasia not seldom occur in the same thyroid gland.



Fig. 76 Very acute toxic goiter. Died unoperated on in wild delirium; temperature 107 degrees. The epithelium is degenerated in part exfoliated; even the septa are destroyed. The colloid is pale, abundant but indifferent. (From Hertzler, A. E. *Surgical Pathology of the Thyroid Gland*, Philadelphia, 1936, J. B. Lippincott Co.)

Following administration of compound solution of iodine the hyperplastic epithelium — as a rule though not invariably — becomes more nearly normal, high columnar epithelium reverting gradually to the low cuboidal type. The lumina become larger as they are apparently distended by increased secretion and accumulation of colloid. Generally, as an invaluable preoperative medication to induce such involution, Lugol's solution may also be expected to reduce the metabolic rate and alleviate symptoms of toxicity. Prolonged administration of this medication, however, causes an exacerbation of the symptoms of hyperthyroidism.

Warthin (1928) stressed the frequent finding (in some 50 to 60 per cent of cases) of lymphocytes in focal aggregations. There may be definite lymph follicles with active germinal centers and wide collars

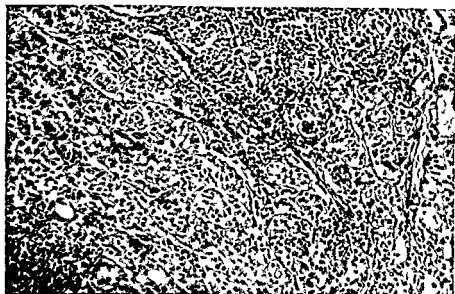


Fig 27 Very acute nonexophthalmic goiter. It is made up of solid masses of cells almost devoid of colloid. The nuclei are small, deeply staining, the protoplasm in some areas syncytial like. Various areas are infiltrated with lymphocytes. (From Hertzler, A. E. *Surgical Pathology of the Thyroid Gland*, Philadelphia, 1936, J. B. Lippincott Co.)



Fig 28 Exophthalmic goiter. Papillary hyperplasias project into the acini. The colloid is crenated, retracted, palely staining. The protoplasm of some of the cells is poorly staining, others are granular indicative of great toxicity. The extensive papillations indicate a high degree of toxicity. (From Hertzler, A. E. *Surgical Pathology of the Thyroid Gland*, Philadelphia, 1936, J. B. Lippincott Co.)

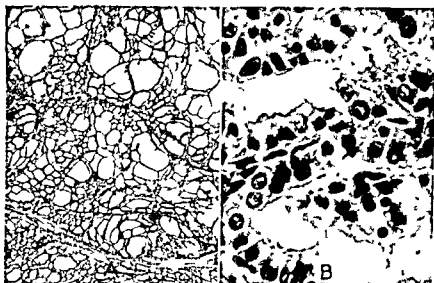


FIG. 22 Acute toxic goiter implanted on a colloid (A) The larger area is made up of large acini in which project new cell formations (B) Acini lined with cuboidal epithelium. The protoplasm is sharply defined, the nuclei deeply staining, both factors indicating an active state. (From Hertzler, A. E. *Surgical Pathology of the Thyroid Gland*, Philadelphia, 1936, J. B. Lippincott Co.)

of small cells of the adult type. In fact, Warthin expressed the belief that the most important histologic criterion of toxic goiter is the occurrence, throughout the thyroid, of hyperplastic primitive lymph nodes with germinal centers giving evidence of lymphoid exhaustion. Further, according to Warthin, a constitutional anomaly, Graves' constitution predisposes the individual at birth to the pathologic reactions noted in Basedow's disease, toxic adenoma, and related conditions—he considered Graves' constitution to be the underlying pathologic and clinical entity of exophthalmic goiter, toxic goiter, and toxic adenoma. Graves' constitution, Warthin pictured as dependent upon the presence of hyperplastic primitive lymph nodes with germinal centers, such nodes occurring throughout the thyroid, the hyperthyroid patient, then, would be regarded as belonging to that group showing the lymphoid constitutionality. Certain other authorities, however, attribute the occurrence of lymphoid tissue to inflammatory reaction.

Formation of Nodules. Isolated nodules may be formed in focal areas of hyperplasia and colloid involution and may be regarded as functional aberrations rather than true tumors, even though they

may present extensive colloid formation, necrosis, cystic degeneration and hemorrhage. Such nodules may be enclosed in a pseudocapsule of connective tissue and show varying degrees of lymphoid activity. Differentiation from true tumors may be increased by the finding of various hyperplastic changes (including extreme degrees of papillary hyperplasia usually associated with typical exophthalmic goiter), acini distended with deep staining colloid, and acini lined by flat, cuboidal epithelium. It has frequently been pointed out that, as a rule the nodules sometimes observed in hypertrophic parenchymatous thyroid or exophthalmic goiter (with or without true adenomas) are distinguishable from true adenomas of exophthalmic goiter by the absence of true capsules, the rare occurrence of the fetal type of acini, and the microscopic resemblance of the nodules to the extra nodular portions of the goiter.

SIGNIFICANCE OF THE STAINING PROPERTIES OF COLLOID

Physiological, clinical, and pathological significance has been attributed to the staining properties of colloid by Hertzler (1941). As he observed, normal colloid is acidophilic and stains pale pink with eosin. Thin colloid stains less intensely and is usually associated with cellular hyperplasia, in toxic goiter, there is some correspondence between the toxicity and decreased ability to take the stain (eosin). In contrast, a thick colloid is indicated by more intense staining, a common characteristic of old goiters, especially when the colloid is in a final phase of deterioration and there is associated degeneration of connective tissue. Hertzler further found that basophilic colloid — colloid taking hematoxylin — may be regarded as pathologic, such colloid is associated with an atrophic epithelium. Old goiters which are the seat of degenerative changes generally possess basophilic colloid as do goiters in patients who suffer heart failure. It is possible that basophilic colloid contains a substance having an adverse effect upon the heart. Acini which contain basophilic colloid may be quite atrophied and permanently functionless.

ADENOMATOUS GOITER

Adenomas are the most common benign tumors of the thyroid gland. Their functional and morphological characteristics undergo a great variety of changes under the influence of physiological factors



Fig 30 Acute toxic goiter established on a simple colloid (a) Small areas of papillary formation and newly developed acini (B) Cells lining the acini are low columnar the protoplasm not sharply defined and the nuclei variously staining The colloid is uniformly staining but pale (From Hertzler A F *Surgical Pathology of the Thyroid Gland* Philadelphia, 1936 J B Lippincott Co)

which may be the same as those affecting the thyroid parenchyma or may be different. According to their structure and histological variations different types of benign adenoma are recognized: embryonal, simple, fetal, intermediate or colloid adenoma. We may encounter in a single adenoma any or all of the features of these various types. Degree of differentiation serves as a basis upon which we can classify the adenomas. In the embryonal adenoma, little or no evidence of follicle formation is to be seen. Such a tumor is made up of cords and trabeculae of epithelium, lumina being sparse or absent and colloid being completely absent. In the follicular type of fetal adenoma, acinus formation is in an early stage: the acini are few and scattered; their epithelial cells are low and flat cuboidal, and colloid secretion and accumulation is just beginning. According to a number of authorities, fetal adenomas take their rise from fetal rests, but, in the present state of our knowledge of these growths, we are able only to emphasize the point that the term fetal adenoma indicates a tumor characterized by an extremely hyperplastic type of cellular arrangement, an



Fig 31 Nodular toxic goiter



Fig 32 Goiter removed from girl 17 years of age (A) External view of normal appearance and consistency (B) Nodule within

arrangement similar to that typical of the fetal thyroid gland. It is true, however, that the histology of these tumors varies greatly, and widely differing degrees of differentiation are to be seen. Well developed follicles may be said to be characteristic of the simple adenoma. In the colloid adenoma, all the follicles are widely distended with secretion. Hence the clinical

and pathological differentiation of adenomas from nodules of endemic or simple colloid goiter may at times be difficult, the nodules in endemic goiter show excess storage of colloid or compensatory formation of new follicles, or — as in most instances — both changes.

The term "discrete adenoma" is applied to solitary, well differentiated tumors having a structure and consistency markedly different from the corresponding features of the remainder of the thyroid gland, they may be hyperplastic or in colloid phase. They may occur, though rarely, in an otherwise normal gland, or as a distinctly localized growth in a colloid goiter. Such a tumor may, further, be the only well-differentiated adenoma in a multiple adenomatous goiter (nodular

goiter) There is no certain means of differentiating between a fetal type of discrete adenoma and an early carcinoma

All adenomas are encapsulated They vary widely in size and differ greatly in consistency, some being soft and others firm Their color ranges from light amber to reddish brown Various types of degenerative changes are frequent hemorrhagic, fibrous, cystic, hyaline, (lipoid), granular and calcareous Microscopic examination discloses that the general arrangement, size and shape of epithelial cells in adenomas differ not only in different adenomas but also in different areas of the same adenoma We frequently observe fetal acini along with well developed acini *some of which contain no colloid, whereas others are distended with secretion*

Adenomas associated with the hypertrophic parenchymatous thyroid gland of exophthalmic goiter often possess columnar epithelium which may show a papillary like infolding, such microscopic architecture is less often seen in toxic adenoma and rarely in nontoxic

Macroscopic differentiation between toxic adenoma and non toxic adenoma is impossible, and even the microscopic differentiation is not seldom extremely difficult Still, a prominent columnar epithelium is in general characteristic of toxic adenoma We agree with other authors that the degree of toxicity may in many cases be indicated not only by the number and size of adenomas present in the thyroid gland but also by the amount of columnar epithelium A microscopic diagnosis of toxic adenoma depends upon the finding that the columnar epithelium showing papillary infolding is restricted to the adenoma and does not occur in the other non adenomatous portions of the gland, which should not present the microscopic picture of exophthalmic goiter and should be practically normal

RELATION OF ADENOMAS TO MALIGNANCY

Adenomas may give rise to malignant growths It is believed that some 80 per cent of thyroid cancers take their rise from pre existing adenomas Estimates are that a malignant tumor arises from an isolated nodule in the thyroid about ten times more often than from any other type of thyroid enlargement (Warren, 1911, Ward, 1911, Cole et al, 1915, Hinton and Lord 1915) According to Portmann (1911) not only are malignant adenomas the most common type of malignant tumor of the thyroid but about 90 per cent of the epithelial malig

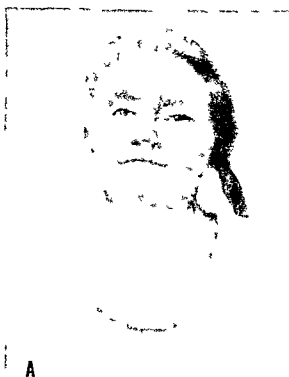


Fig 33A Large mono-cystic tumor of thyroid Patient aged 68 years Front view

Fig 33B Lateral view

Fig 33C. Same on morning of third day following operation

nant tumors of the thyroid gland originate in pre existing adenomas " The consensus today is that most cancers of the thyroid gland originate in a discrete embryonal or fetal adenoma which is primarily benign, remains benign for various periods of time and later becomes malignant *Excluding tumors into which hemorrhage has occurred, firmness within an adenoma should strongly suggest malignant degeneration within the tumor (Lahey, 1911)* Any change in the consistency of the tumor should bring to mind the possibility of malignant degeneration within the capsule When malignant degeneration takes place and the fibrous capsule is eroded and penetrated, the discrete outline of an isolated adenoma may be lost Further, when a movable discrete adenoma becomes fixed, the fixation may be the result of malignant degeneration accompanied by perforation of the capsule, the tumor then becoming adherent to the trachea or other adjacent structure Paralysis of the recurrent laryngeal nerve on the same side as the lobe in which an isolated adenoma has long existed should also arouse suspicion of malignant degeneration, perforation of the capsule and involvement of the recurrent laryngeal nerve Because most cancers of the thyroid gland take their rise in discrete adenomas, the enlargement we would expect in such cases is local (unilateral), the contour of the gland thus being lost Such enlargement is to be regarded as typical but by no means invariably characteristic Another important diagnostic point is the early involvement of the lymph nodes

Recent papers have stressed the possibly surprising incidence of cancer among patients with nodular goiter Ward (1911) found an incidence of 4.8 per cent in 3,539 nodular goiters of both sexes



Fig. 34A and B ($\times 200$) Medium sized artery of capsule showing the sclerosis which is found in involuted Graves type thyroid even in very young individuals Elastic tissue stain



Fig 35 (x 160) Tubular fetal adenoma of thyroid

Among females, the incidence was 4.0 per cent, but among males 11.0 per cent. In Ward's series of 1,900 toxic diffuse goiters, there was only one instance of cancer. Broders and Parkhill (1944), however, pointed to a new danger, one arising from modern chemotherapy of Graves' disease. Microscopically the thyroid gland in cases of Graves' disease treated with thiouracil shows extreme hyperplasia with heightened epithelium, marked papillary infolding and mitosis of the epithelial cells. The thiouracil goiter is more of a cellular hyperplasia with mitosis very much in evidence, and so therefore more comparable to a carcinoma of the thyroid. Cole and associates (1945) indicated the incidence of cancer in 523 nodular goiters—toxic, non-toxic, benign and malignant—to be about 7.2 per cent. Of greater significance, however, is the breakdown of their determinations thus briefly summarized: in 195 cases of non-toxic nodular goiter

there was an incidence of 17.1 per cent of cancer whereas in the group of non toxic solitary nodules cancer was detected in 24 per cent. Hinton and Lord (1915) reviewed the cases of nodular goiter in which they, operated during a 5 year period, after eliminating all instances in which the diagnosis of cancer was made preoperatively and confirmed pathologically they still were able to cite 184 cases of clinically benign nodular goiter some toxic and some non toxic in which pathologic examination disclosed an incidence of 7.6 per cent of cancer. These authors remarked that their figures are in close agreement with those of Cole and co workers (1915). They express the belief that 'an incidence of 7.6 per cent of cancer in cases of apparently benign nodular goiter is a compelling reason for operative removal of all such nodules unless a strong contraindication exists. We agree that a non toxic nodular goiter—be it single or multiple—should be removed surgically, the incidence of unsuspected cancer is definitely high in such cases. Moreover, toxic nodular goiter should not be treated with thiouracil but should also be removed surgically. The possible dangers of treating these goiters with thiouracil has been discussed in another section (see page 158). Ward (1944) in contrast, notes that the potential danger of thiouracil therapy in toxic *diffuse* goiter is slight.

MALIGNANT TUMORS

Histopathological Classification Authorities are still far from general agreement concerning the histopathological classification of malignant tumors of the thyroid gland. Graham has suggested the following classification:

- I Sarcomas
 - (a) lymphosarcoma
 - (b) spindle-cell sarcoma
 - II Mixed tumors
 - (a) carcinoma sarcoma
 - III Carcinomas
 - (a) scirrhous carcinoma
 - (b) adenocarcinoma
 - (c) papillary carcinoma
 - (d) malignant adenoma
- } not arising in adenomas
 } arising in adenomas

In addition, Graham has recognized and described not only lymphosarcomas and fibrosarcomas but other (rare) types of connective tissue

neoplasms as well, having the same histopathological and clinical characteristics as sarcomas of similar histogenesis encountered in other organs

Warren (1941) in common with other authors has observed that in the classification of thyroid tumors there is an opportunity for the correlation of certain types of clinical behavior with certain morphological entities — although proposed classifications based on assumptions of etiology have not been found satisfactory or notably enlightening. Indeed — to state a truism — not yet has it been found possible to elucidate the origin of any type of thyroid tumor, benign or malignant

In certain groups of thyroid tumors morphologic features and clinical behavior may at times show some correlation (Haagensen 1931, Clute and Warren, (1931-1935) Warren (1941) proposed the following classification of thyroid tumors

Benign

- (1) Adenoma (a) embryonal, (b) fetal (c) simple, including the Hurthle cell type, (d) colloid adenoma
- (2) Papillary cystadenoma (a) arising from the thyroid gland and (b) arising from aberrant thyroid tissue

Malignant

Group I — Low or potential malignancy

- (1) Adenoma with blood vessel invasion
- (2) Papillary cystadenoma with blood vessel invasion
 - (a) arising from the thyroid gland
 - (b) arising from aberrant thyroid tissue

Group II — Moderate malignancy

- (1) Papillary adenocarcinoma
- (2) Alveolar adenocarcinoma
- (3) Hurthle cell adenocarcinoma

Group III — High malignancy

- (1) Small cell carcinoma (carcinoma simplex)
 - (a) compact type
 - (b) diffuse type
- (2) Giant cell carcinoma
- (3) Epidermoid carcinoma
- (4) Fibrosarcoma
- (5) Lymphoma

Ward (1944) has essayed a decided simplification of the systematic description of malignant tumors of the thyroid gland, his grouping is based on observations that papillary tumors of the thyroid would appear to offer the most favorable prognosis under modern therapeutic conditions, as follows. Ward has placed all papillary tumors of the thyroid in a separate group, whether or not such tumors take their origin in adenomas, aberrant thyroid tissue, or the thyroid gland proper. The presence and proportionate quantity of papillomatous tissue in the thyroid, according to Ward, determine the prognosis, including the response to radiation therapy, further, few carcinomas of the thyroid gland present a distinct cellular pattern. Then the practical classification, from a prognostic and therapeutic viewpoint, would be roughly

Group I Papillary carcinomas

Group II Malignant adenomas

Group III All other malignant growths, including scirrhus, small cell and large cell types, undifferentiated carcinomas and carcinomas displaying sarcomatous tendencies

Group I of Ward's classification would seem to present no unusual problem in differentiation. Adenomas showing malignant degeneration — as determined by gross findings — would be placed in Group II, this group is subdivided by Ward into (a) Langhans struma — the proliferating adenoma as described by Langhans, and (b) fetal adenomas — all other malignancies arising in an adenoma — and so classified for lack of a more descriptive term.

Incidence The recorded incidence of malignant lesions of the thyroid gland has varied according to the criteria of malignancy accepted by different clinics and according to geographical region, the incidence being higher in regions where goiter is endemic. In 1921, Speese and Brown reported that cancer had been present in 4.6 per cent of their cases of goiter, a higher incidence than that noted by the majority of authors. At the Massachusetts General Hospital, of 606 unselected cases of goiter, a proved malignant process was found in 1.3 per cent of cases, if toxic goiters are excluded from this series, the incidence of malignancy in the remainder becomes 2.0 per cent, and if only nodular goiters are considered, the incidence of cancer becomes 3.2 per cent. In a series in which thyroidectomy was performed 1750 times, the incidence of malignancy was found to be

13 per cent by Welti and Huguenin (1939) Lahey, Hare and Warren (1940) noted that 231 cases of carcinoma of the thyroid gland were encountered in 18,600 operations for goiter—an incidence of 1.2 per cent. In the Cleveland Clinic series reported in 1940, 289 malignant tumors of the thyroid gland were seen in 17,021 thyroidectomies, the incidence being 1.69 per cent. In this series, 3 per cent of all nodular goiters were malignant. Pemberton (1939, 1941) has observed that, at the Mayo Clinic, the percentage of malignant tumors of the thyroid gland encountered in cases of goiter increased from 2 per cent in 1919 to 4.9 per cent in 1937. Pemberton states that this increase is only apparent. In recent years, malignancy has been recognized at an earlier stage. An incidence of 3 per cent, with 169 malignancies in 5,439 surgical cases of goiter, was recorded by Ward (1944).

Incidence and Geographical Region Malignant tumors of the thyroid gland occur with higher frequency in regions where goiter is endemic (Wegelin, 1928, Ward, 1935). In Switzerland, the incidence of malignancy in surgically treated goiters has been reported to vary from 6.5 to nearly 10 per cent (Kocher, 1907, DeQuervain, 1935), whereas in Canada the incidence was found by Eberts and associates (1929) to be less than 1 per cent. According to Wilson (1921), autopsies in Bern, Switzerland, showed that one death in about every 93 resulted from malignant goiter as contrasted with one death from the same cause in about every 928 deaths in the United States. In this country, the incidence of malignancies in surgically treated goiters appears to range between 1.2 per cent (Lahey, Hare and Warren, 1940) and 4.9 per cent (Pemberton, 1939). The prevention of endemic goiter will, we believe, lower the incidence of primary malignant lesions of the thyroid gland. Ward (1935) noted that in regions in which the incidence of endemic goiter is high, non-papillary types of adenocarcinoma of the thyroid gland predominate, whereas in regions in which goiter is not prevalent, papillary types of adenocarcinoma of the thyroid gland predominate. The papillary type of adenocarcinoma is less malignant than the non-papillary types, hence malignant goiter has a better prognosis in regions where goiter is not endemic than in regions where it is endemic.

Age Incidence Less than 20 per cent of cases of malignant tumor of the thyroid gland occurs before the age of 40 years. About two-thirds of the cases occur between the ages of 40 and 70 years. Thus

the age incidence of cancer of the thyroid gland corresponds closely to that of malignant neoplasms of other organs. In Pemberton's series (1939) of 774 cases 539 patients, or 69.6 per cent, were between 40 and 70 years of age, the mean age for females was 48.1 years, whereas it was 52.8 years for males. Ward (1935) reported an average age of 52.7 years in his group of 95 patients with malignant tumor of the thyroid gland.

Malignant Lesions of the Thyroid Gland in Childhood In a series of 137 cases of surgically treated goiter in children up to the age of 15 years, the incidence of malignancy was found to be 9 per cent (12 cases) by Kennedy (1940). Excluding the cases of exophthalmic goiter, 12 cases out of 27, or 44 per cent, were cases of malignant lesion. Kennedy stressed the point that any mass of the thyroid gland in children should be suspected of possessing malignant characteristics. Carcinoma would seem to have a greater predilection for the thyroid gland in early life than is generally believed, according to Pemberton in whose series (1939) of 774 cases of malignant lesions of the thyroid there were 17 patients less than 20 years of age. Hence operation for the removal of thyroid nodules among children should not be deferred as some clinicians and surgeons have advised. A large percentage of the malignant lesions which are encountered in the thyroid gland in early life are of the papillary or malignant adenomatous type, and the malignancy is of a low grade and, in the early stages are especially amenable to treatment by surgery or irradiation.

Sex Incidence In the 88 cases of malignant tumor of the thyroid gland studies by Welti and Huguenin (1939), there were 18 male patients and 70 females a ratio of 1:3.9. In the series of Pemberton (1939), of the 774 patients with thyroid cancer, 282 were males and 492 were females, a ratio of 1:1.74. For the same period 1907-1937, the ratio of males to females among the patients who had all types of benign nodular goiter, exclusive of exophthalmic goiter, was 1:5.07. Watson and Pool (1940) found that there were 117 females to 50 males in their group of 167 cases of cancer of the thyroid gland. Thus, in cases of nodular goiter, the probability of the occurrence of malignancy is much greater in males than in females. Ward (1941) noted that the incidence of malignancy was 4.8 per cent in 3,539 nodular goiters of both sexes, in females, the incidence was 4.0 per cent, whereas in males it was 11 per cent.

Incidence of Different Histopathological Types The most frequently occurring malignant tumors of the thyroid gland are malignant adenomas, papillary carcinomas and adenocarcinomas not arising in adenomas. Mixed types and sarcomas are of comparatively rare occurrence. In Pemberton's series (1939) of 774 cases of malignant lesions of the thyroid gland, there were 197 patients who had malignant adenoma (adenocarcinoma in adenoma), or 38 per cent of the 517 cases in which pathological examination of the tumor was made. Diffuse adenocarcinoma was found in 157 patients or 30.4 per cent of cases. Papillary adenocarcinoma was encountered in 155 patients, or 30 per cent. There were only 4 cases of sarcoma, one of which was a case of primary osteogenic type. Primary squamous epithelioma was encountered in four cases also. Watson and Pool (1940) reported the incidences of different types of thyroid cancer in their series of 167 cases as follows: adenocarcinoma, 34 per cent, small, alveolar, and large cell adenocarcinomas (Grades 2 and 3 and Huerthle cell type), 27 per cent, adenocarcinoma (ungraded), 15 per cent, spindle and giant cell adenocarcinoma, 13 per cent, small round cell carcinomas, 5 per cent, lymphosarcoma, 3 per cent, metastasizing struma, 3 per cent.

Portmann (1941) somewhat differently classified 220 consecutive cases of malignant tumor of the thyroid gland according to histopathological type. He found that 67.3 per cent of the cases were histopathologically classifiable — i.e., in these cases the type of neoplasm could be ascertained microscopically. Another 7.7 per cent were unclassifiable histopathologically: the tissues were examined microscopically and the presence of malignancy was proved, but the type of malignancy involved could not be determined. Hence 75 per cent of the cases were histopathologically malignant. Twenty-five per cent of the cases were tabulated as histopathology unknown, the diagnosis of malignant tumor being based on obvious clinical manifestations because the disease was far advanced and operation or biopsy was deemed inadvisable. Portmann based the percentage incidence of the different histopathological types upon the total histopathologically classifiable, 148 cases, or 67.3 per cent. Eighty of the tumors were malignant adenomas (54.0 per cent of 148 cases), 24 cases (16.2 per cent) were adenocarcinomas not originating in adenomas, 21 tumors (14.2 per cent) were papillary carcinomas, and

13 (9 per cent) were lymphosarcomas. In addition, there were 3 cases of scirrhus carcinoma, 4 cases of fibrosarcoma, and 1 case of each of the following types: carcinoma sarcoma, myosarcoma, and rhabdomyosarcoma. Portmann remarked that, if the questionably malignant adenocarcinomas not originating in adenomas are included in the group of tumors of epithelial origin, then approximately 80 per cent of the epithelial neoplasms would be found to have originated in pre-existing adenomas (malignant adenomas and papillary carcinomas).

MALIGNANT ADENOMAS

So-called benign adenomas give rise to most (perhaps more than 90 per cent) of the epithelial malignant tumors of the thyroid gland, including both malignant adenomas and papillary carcinomas. Some 80 per cent of malignant adenomas take their rise in these pre-existing benign adenomas, and for the most part, in fetal adenoma. Ward (1914) has remarked that such primary malignant goiters grow slowly or remain dormant for long periods and, further, if a tumor has existed for years in the thyroid gland and is found to be malignant after its surgical removal, the growth may not have been benign at its inception.

In the transition to frank malignancy, both malignant adenoma and papillary carcinoma enlarge within the capsule of the pre-existing adenoma, erode the capsule and perforate it, and then invade surrounding structures. Most authorities have accepted Graham's criterion of malignancy: the invasion of blood vessels. The histological picture presented by the tumor and also the invasion of the capsule of the adenoma, of surrounding thyroid tissue, adjacent muscles of the neck, and the lymphatics are additional, recognized manifestations of malignancy.

Thus, growth characteristics of the tumor are of outstanding significance. Malignancy is not necessarily revealed by histological study of the tumor, regardless of its microscopic pattern, an encapsulated tumor cannot be regarded as definitely malignant unless its invasive tendency has become obvious. Both malignant adenoma and benign adenoma show numerous, wide morphologic variations. The gross appearance of the malignant adenoma may be very similar to that of a benign adenoma. Histologically, the malignant growth may show

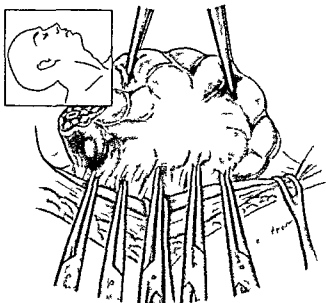


Fig 36 Drawing made at time of operation of sclerosing carcinoma of the thyroid gland

variations ranging from the pattern of a frank undifferentiated cancer to that of a well differentiated, apparently benign adenoma — which, as in the instance of so called benign metastasizing struma, may indicate its malignant tendencies only by limited metastasis through the blood stream. Malignancy may be suggested by the cellularity of the tumor and the absence of colloid, confirmation may be forthcoming from the gross finding thyroid tissue filling the capsular vessels. No characteristic morphology distinguishes the malignant adenoma. In a single tumor, the following structures may be observed, in varying combinations: structures similar to those of adenocarcinoma, papillary carcinoma, medullary carcinoma, and sarcoma like carcinoma. In some cases, the structure of the follicles is preserved in whole or in part, in others the follicular arrangement is completely lost, so that we see only branching columns of undifferentiated cells.

In general, then, histopathology alone does not afford satisfactory means of differentiating malignant adenomas or of classifying them with particular regard to their degrees of malignancy. When sections from the same, presumably malignant adenoma show the outstanding

features of fetal adenoma, colloid adenoma, and apparent scirrhous carcinoma, we must base the diagnosis on the finding of blood vessel invasion, which is characterized by the presence of thrombi or polyps of neoplastic cells within the vessels. Such invasive structures, as a rule but not always, present a histological pattern similar to that of the primary growth.



Fig. 37 Photograph of the same tumor shown in Fig. 36 after removal

Commonly the growth is single but it may be multiple. Metastasis most frequently occurs by way of the blood vessels and may take place early, chiefly to the lungs and bones. Lymph gland metastasis is comparatively rare, at least until the capsule of the tumor is involved. Masses of thyroid tissue in the vessels about the thyroid gland may sometimes be observed at operation. Unless distant metastasis has been discovered, in a great many cases malignancy in these tumors

may not be suspected until after operation, involvement of the capsule does not take place until late in the development of the tumor and the consistency and relative fixation or mobility of the tumor may not undergo manifest change. The great majority of malignant adenomas are of a low grade of malignancy; occasionally, however, they are highly malignant.

PAPILLARY ADENOCARCINOMA

Papillary adenocarcinoma may arise within a cystic adenoma or in the portion of the thyroid gland that is free of adenoma. These growths are primarily encapsulated tumors with a papillary arrangement of the epithelial cells. Some, however, are non encapsulated. Papillary cystadenomas may occur as single or multiple tumors, usually soft and small, exceptionally exceeding 5 cm. in diameter. Histologically they present irregular papillary projections which are covered by a single



Fig. 38 (x 160) Intracystic papilliferous adenoma of thyroid

or columnar epithelium. Sparse acini appear to contain normal colloid. Such tumors may be considered to be benign until they show vascular or capsular invasion. Although almost indistinguishable histologically from these so-called benign papillary adenomas, papillary adenocarcinomas generally present the recognized features of malignant transformation. In varying degrees the cells of the malignant tumor exhibit

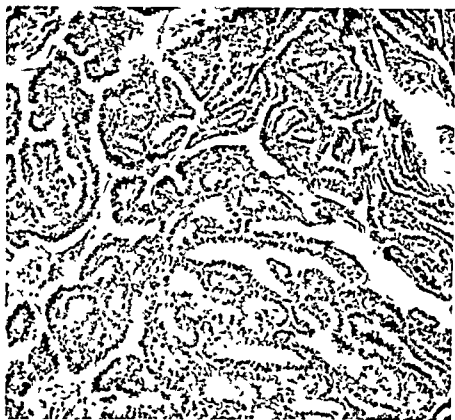


Fig. 39 (x 160) Papilliferous carcinoma of thyroid

anaplastic inversion and invasion of the capsule and stroma. We may encounter mitotic figures here and there. At the inception of malignant tendencies the epithelial cells proliferate, break through the thin stroma at the base of the acini, and finally invade surrounding tissues.

These tumors are most frequently of a low grade of malignancy; they grow slowly and may be present for a considerable period before they invade adjacent tissues. Their comparatively low grade of malignancy has been attributed to their development in encapsulated cysts.

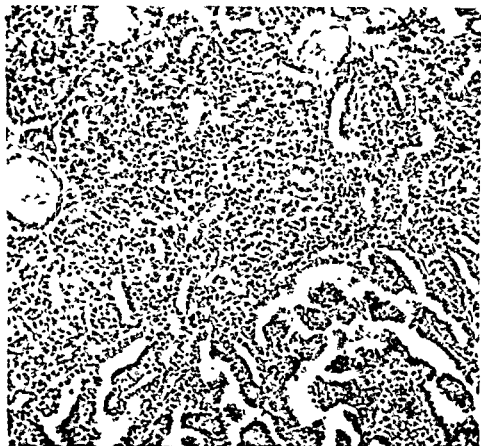


Fig 40 (x 160) Carcinoma of thyroid, part alveolar, part papilliferous

It is believed that, typically, they metastasize chiefly by way of the lymphatics and that they invade blood vessels less frequently than does any other type of neoplasm within the thyroid gland

They often invade the lymph nodes and spread to involve a cervical lymph node or a chain of nodes. Metastasis rarely extends beyond the mediastinum or the lungs even in neglected cases or in cases of recurrence when the lesion may be inoperable because of fixation. The metastatic tumor may be so much larger than the primary tumor that, at operation, the primary tumor may be overlooked if the nature of the cancerous nodules is not recognized. Although some papillary adenocarcinomas tend to recur locally, in early cases complete local excision may be expected to effect a permanent cure. These tumors are radiosensitive.



Fig. 11 (x 160) Carcinoma of thyroid part diffuse, part papilliferous

OTHER TYPES OF ADENOCARCINOMA OF THE THYROID

Adenocarcinoma Not Originating in Adenoma. Graham and certain other pathologists have recognized a variety of tumor which they group as adenocarcinoma not arising in adenoma. These neoplasms are encountered as nodules which may be microscopic or as large as 1.5 cm. in diameter and which present extremes of histopathological variation, in many respects resembling different types of goiter or cancer histopathologically. According to Portmann (1911) "they are unrecognizable clinically, cause no signs or symptoms and are discovered only after removal of thyroid tissue for supposedly benign goiters; their course is unknown and in our experience no patient has developed metastases or died from this type of tumor." In view of the fact that such carcinomas comprised some 16.2 per cent of the histo-

pathologically classifiable tumors of Portmann's series of 220 cases of malignant lesions of the thyroid gland, it must be assumed that other pathologists would have classified many if not all of these neoplasms as other types of carcinoma, such as small round cell carcinoma, spindle cell carcinoma, or perhaps diffuse adenocarcinoma recognized by Pemberton and Lovelace (1941)

Diffuse Adenocarcinoma. Pemberton and Lovelace (1941) have observed that diffuse adenocarcinoma may originate within a pre existing benign adenoma in a thyroid gland or in a nongoitrous thyroid gland. These authors state that this type of tumor presents as wide a variety of cellular changes and histologic patterns as tumors of similar grades of malignancy situated elsewhere. In diffuse adenocarcinomas of the higher grades of malignancy, the follicular structure may be completely absent and the arrangement of the rapidly growing



Fig. 42 (x 160) Carcinoma of thyroid with tendency to squamous metaplasia

cells — small, round, spindle shaped or giant — may suggest sarcoma. Such highly anaplastic growths constitute acute, fulminating malignant lesions of the thyroid gland, metastasis taking place through lymphatic vessels, blood vessels, or both. This type of tumor made up 30.4 per

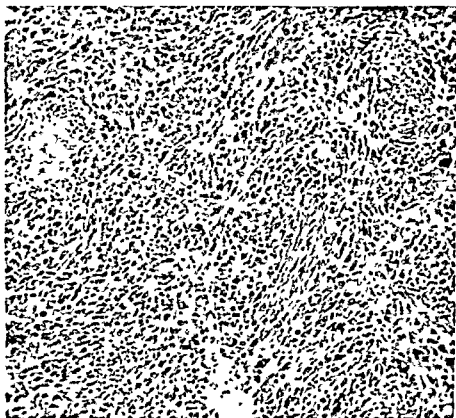


Fig. 13 (x 160) Carcinoma of thyroid diffuse spindle cell type

cent of Pemberton's series (1939) of 774 malignant lesions of the thyroid gland. Pemberton and Lovelace believe that because of the pronounced tendency of these tumors to involve surrounding structures such malignant lesions are more readily recognized clinically than malignant adenomas and papillary adenocarcinomas.

Small Round Cell Carcinoma. Small cell carcinoma, or carcinoma simplex, is the most frequently encountered of the tumors of high malignancy. Two forms are observed: (1) the compact type, in which the cells are closely massed, and (2) the diffuse type, in which the cells are spread irregularly through the thyroid tissue. Histological

differentiation between the diffuse type of small cell carcinoma and lymphomatous involvement of the thyroid gland may be difficult. These highly anaplastic tumors are responsive to irradiation.

Scirrhus Carcinoma Some authors have suggested that scirrhus carcinoma always arises in a pre-existing adenoma, but the actual origin of these tumors has not yet been demonstrated. Frequently these carcinomas destroy the thyroid structure to such an extent as to obscure all evidence of their origin. In common with scirrhus adenocarcinoma elsewhere these neoplasms show prominent desmoplasia. They are not encapsulated. Although they grow slowly, they have highly invasive tendencies, progressing generally by way of the lymphatics into surrounding tissues. Scirrhus carcinoma of the thyroid gland usually kills the patient by local invasion before metastasis can take place. Treatment either by surgery or irradiation is quite ineffective.

Epidermoid Carcinoma This highly malignant type of neoplasm is of definitely exceptional occurrence. At times encountered in early decades, these tumors are believed to arise either from thyroglossal duct epithelium or from thyroid epithelium proper by metastasis.

CARCINOMA SARCOMA (GIANT CELL CARCINOMA)

The infrequently occurring group of malignant tumors of the thyroid gland the carcinoma sarcomas, or giant cell carcinomas have been considered by many writers to be of mixed origin. Both the epithelial and mesothelial elements appear to have undergone malignant change so that we observe the apparently mingled characteristics of carcinoma and sarcoma. Other authors have long regarded these tumors as forms of sarcoma, whereas still others have found transitional areas showing seemingly definite origin from acinar cells. These neoplasms are of high malignancy, extremely anaplastic and rapidly growing, and highly vascular. In most of these tumors no suggestion of the architecture of the thyroid is to be found. Tumor giant cells with multilobulated, hyperchromatic nuclei are characteristic. These malignant growths exhibit a great tendency toward perivascular proliferation of the thyroid cells and subsequent necrosis in areas at a distance from the blood vessels. This type of tumor generally occurs in the later decades, particularly in patients who have long had a nodule in the thyroid, the nodule suddenly beginning to grow rapidly. Extending by

rapid local invasion of the tissues of the neck, carcinoma-sarcomas usually kill the patient by local involvement before metastasis has been conspicuous. In contrast with other anaplastic tumors of high malignancy, these neoplasms are resistant to irradiation.

SARCOMA

In rare instances, malignant degeneration takes place in the abundant lymphatic tissue and fibro elastic stroma of the thyroid gland, to give rise to sarcoma. Lymphosarcomas of the thyroid gland are similar histologically to the same type of neoplasm in other organs and have the same developmental characteristics and clinical course. They grow rapidly and are usually in advanced stages before therapeutic procedures are instituted. These tumors are not surgically curable and although they are radiosensitive, good results are seldom obtained.

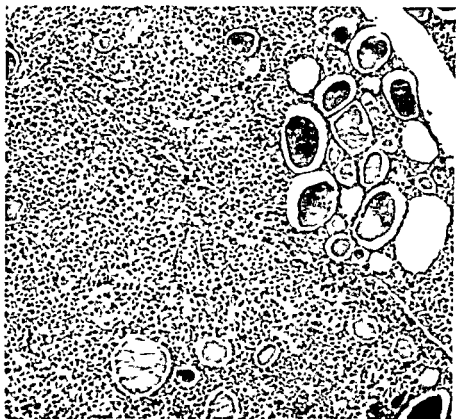


Fig. 11 (x 160) Reticulum cell lymphosarcoma of thyroid

by roentgen treatment. All four patients in Pemberton's series (1939) of 774 cases of malignant lesions of the thyroid gland died within a year after operation. Combined surgical and roentgen treatment of this condition serves to prolong life. Portmann (1941) reported that none of the patients with lymphosarcoma in his series of 220 cases of thyroid cancer lived five years following operation alone but four patients out of nine who received postoperative roentgen therapy remained well for five years or more, and three of these patients were apparently cured.

True fibrosarcoma of the thyroid gland is very rare. A number of the reported cases of fibrosarcoma appear to have been cases of giant cell carcinoma. Grossly and histologically as well as clinically it resembles fibrosarcoma in other organs. This type of tumor of the thyroid gland is incurable surgically and is resistant to irradiation. Local involvement results in the death of the patient.

OPERABILITY, MEASURES OF TREATMENT, AND PROGNOSIS

The operability, principles of treatment, and prognosis in malignant lesions of the thyroid gland depend not only upon the type of tumor but also largely upon the extent of involvement at the time treatment is instituted. Obviously, a localized tumor in an early stage is more readily treated and has a better prognosis than growths which have extended beyond the capsules of the gland. Neoplasms in the earliest stages (small adenomas, for instance) may not give rise to any clinical evidence of their presence and may be discovered only after histological examination of tissue removed. In such instances of course, the condition has been successfully dealt with even before it was recognized. Indeed, it may be stated as a general principle, that if we wait until the diagnosis of cancer can be made clinically, in all probability we have waited until the time for surgical cure has passed. For as a rule the diagnostic signs and symptoms definitely indicating malignancy appear only after perforation of the capsule of the gland and involvement of surrounding structures. Huskiness of the voice and fixation and hardness of the thyroid gland may be associated with benign adenomatous nodules but when these signs are present we may not safely ignore the possibility of malignancy. In the case of malignant tumors, hoarseness is caused by infiltration of the recurrent nerves; fixation is brought about by involvement of the trachea or ribbon

muscles, and hardness results from outward growth of neoplastic tissue to replace normal, soft tissue

Discrete Adenomas The danger of malignancy in discrete adenomas is so great that they should be removed as soon as they are discovered, no matter how small the growth or how young the patient. Even a very small discrete adenoma may be malignant, and malignancy in such adenomas may eventuate in childhood and result fatally. A discrete adenoma is encapsulated and the thick fibrous capsule has a distinct outline. When the capsule is eroded and perforated as a result of malignant degeneration the outline becomes less distinct, any such change should suggest the possibility of malignancy. Further, loss of mobility or fixation of an adenoma may be caused by hemorrhage within the tumor and the production of exudate about the tumor or by malignant degeneration with perforation of the capsule and involvement of surrounding structures. Highly suggestive also is suddenly developing hoarseness of the voice after a discrete adenoma has been present for some time, when laryngeal examination discloses paralysis of the recurrent laryngeal nerve on the same side as the tumor, we have additional evidence pointing to the possibility of penetration of the capsule and involvement of the recurrent laryngeal nerve by malignant growth. Operative treatment is generally recommended on such presumptive evidence. The uninvolved lobe also should be thoroughly explored for other nodules by palpation and in case of doubt an exploratory incision should be made. No encapsulated nodule should be allowed to remain in the thyroid gland once malignant degeneration has been suspected or actually demonstrated in a discrete adenoma. Today, the majority of authorities are convinced that benign fetal and embryonal adenomas should be removed before they become malignant.

Operability In the 88 cases of malignant tumor of the thyroid gland studied by Welt and Huguenin (1939) radical surgical operation could be performed for only 21 patients. Watson and Pool (1940) found it possible to carry out operative procedures in 51 of the 167 cases in their series, 70 per cent of the lesions were considered to be inoperable. Watson and Pool also determined that there was evidence of metastatic involvement in 37 per cent of their cases and noted evidence of obstruction to the upper air passages of upper food passage ways in 11 per cent.

Portmann (1941) in his study of 220 patients with malignant tumor of the thyroid gland who were examined at the Cleveland Clinic, observed that 70 of the cases were in advanced stages of the disease, 9 per cent (20 cases) being in too advanced stages of the disease to be treated

At the Mayo Clinic, 1907-1938, 774 patients were found to be suffering from malignant lesions of the thyroid gland, and operative procedures were carried out for 509. From 384 of these 509 cases the tumor was extirpated, and in 125 cases one or more of the following procedures was employed: biopsy of tissue from the gland or from metastatic masses, excision of involved lymph nodes, tracheotomy for obstruction. The 384 patients who were subjected to partial thyroidectomy represented 49.6 per cent of the 774 cases seen during the 31 year period (Pemberton, 1941).

Broders (1941) and Portmann (1941) have stressed the significance of the grade of malignancy as a factor in determining operability. Broders' method of grading is based upon differentiation of cells. According to this method, cancers in which about 75 per cent of the cells are differentiated and about 25 per cent undifferentiated are included in grade 1. In Broders' revised system (1941) the mitotic figures and cells with prominent nucleoli are considered only as undifferentiated cells. Cancers of grade 2 present a differentiation ranging from 75 to 50 per cent, the undifferentiation ranging from 25 to 50 per cent. A grade 3 cancer has a differentiation ranging from 50 to 25 per cent and an undifferentiation ranging from 50 to 75 per cent. In grade 4 are grouped the cancers showing differentiation ranging from 25 per cent to practically nothing and undifferentiation from 75 per cent to practically 100 per cent. This grading is based solely on the microscopic study of the cancer cells themselves and not on clinical history or ultimate result. In the series of malignant lesions of the thyroid gland studied at the Mayo Clinic from 1907 to 1937, the grade was determined according to Broders' method in 496 cases. In grades 1 and 2 there were 338 tumors, 284 of which were operable (84 per cent). There were 72 tumors of grade 3, and fifty-two or 72.2 per cent were operable. In grade 4, 86 tumors were encountered, and only 46, or 53.5 per cent, were operable (Pemberton, 1941).

Two factors are of pre-eminent importance in determining operability: (1) extent of local invasion of surrounding tissues by the

primary lesion, and (2) the presence or absence of distant metastasis. Extent of local invasion is indicated by the relative fixation of the tumor. It is generally agreed that tumors which are firmly adherent to all contiguous structures must be regarded as inoperable, the risk of removing such a tumor is out of proportion to the benefit which could possibly be expected. Moderate restriction of the mobility of the tumor may indicate that perforation of the capsule of the gland has been limited to a single, more or less distinct site. Because of the possibility that, under such conditions of localized invasion, the tumor may be entirely extirpated, then surgical exploration would seem to be indicated. Even if it is found that the tumor cannot be completely removed, benefit may be derived from the application of radium to the remnant of the carcinoma.

Hare (1911) noted that in a number of instances inoperable tumors were rendered operable by radiation treatment, the tumor dose was 4,800 r or less when the radiation was given by the protracted method. Other tumors which were recurrent were kept inactive over a period of 5 to 7 years by similar radiation treatment. In the treatment of relatively anaplastic tumors radiation treatment was given postoperatively in all cases following as complete surgical removal as possible, these tumors invade locally, are widespread and frequently metastasize to the lungs. With the exception of the giant cell tumor which is highly resistant to radiation, the anaplastic tumors are radio-responsive. Hare found that the radio-responsive types of anaplastic, highly malignant tumor became clinically inactive in the region treated when 1,800 r had been delivered to the tumor bed. As soon as the patient's condition was favorable, radiation treatment was directed to the entire tumor bed, both lobes of the thyroid gland and adjacent lymph structures in the neck were also treated at the same time. In Hare's procedure, the neck was divided into 3 portals, 1 on each side and 1 in the midline. A total of 2,000 r was given to each portal in a period of 21 treatment days. A better response was obtained by this method which involves treating the entire tumor bed daily with cross fire radiation, and there were less skin reaction and less irradiation sickness. Papillary adenocarcinomas are radio-responsive and radio-curable, according to Hare, whereas the alveolar adenocarcinomas are generally resistant to irradiation, as shown by the small percentage of 5 year survivals (27 per cent). In the group of patients with papillary

adenocarcinomas treated by irradiation the 5 year survival rate was 80 per cent

Pemberton (1941) recommended that if, on surgical exploration, the local neoplasm is found to be too adherent or fixed for resection, radium needles may be buried, 1 cm apart, in the tumor. Silk threads are attached to the needles to permit closure of the surgical incision, the needles are removed aseptically after a period of from 24 to 48 hours. Each needle contains 1 mg of radium and the filter is 0.4 mm of platinum. If the tumor is not definitely encapsulated, Pemberton advocated, a large rubber drainage tube should be left in the cavity. Twelve to 48 hours later it is possible to insert radium (on a lead stem) into the depths of the cavity. In every case, during convalescence and after partial healing of the wound, topical application of radium is employed as well as treatment with roentgen rays.

We would like to emphasize, in common with most authors that in a great many instances the malignant nature of the lesion may not be suspected before operation. Usually the operable malignant lesion is completely encapsulated. Pemberton (1939) and certain other surgeons have stated that removal of such tumors, with a definite margin of safety is to be considered a sufficiently radical procedure. Hertzler (1942), however, has strongly advocated total thyroidectomy. Pemberton believed that it is only for a very limited group of bilateral infiltrating carcinomas that thyroidectomy is indicated, with subsequent irradiation. If the carcinoma is not definitely encapsulated, the operative procedure should include not only total removal of the lobe involved but also excision of adjacent adnexa, the amount of non essential tissue removed depending upon the nature and extent of the neoplastic growth in the individual case. Extirpation of the cervical lymph nodes is necessary when there is evidence of their involvement. It is to be remembered that papillary adenocarcinoma commonly spreads by way of the lymph vessels. Radical removal of the primary lesion together with the involved cervical nodes is indicated — surgical interference is not contraindicated in such cases of metastasis, papillary adenocarcinoma commonly having a low histologic grade of malignancy. In other types of carcinoma, after the cervical nodes have become involved, radical removal of the carcinomatous process may not be justifiable. Irradiation may serve to reduce the size of the lesion and hold in abeyance inoperable and recurrent masses of malignant

thyroid tissue, (Hare, 1911, Pemberton and Lovelace, 1911, Lahey, Hare and Warren, 1910)

Operative Mortality In malignant lesions of the thyroid gland, the operative mortality depends chiefly upon the stage to which the disease has advanced the extent of the invasion of surrounding tissues by the tumor and the character of the invaded structures Watson and Pool (1910) reported an operative mortality rate of about 2 per cent (51 cases, 1 fatality) after partial thyroidectomy for carcinoma, where the operative mortality was 50 per cent after tracheotomy in 14 cases in which the patients were encountered late in the course of the disease Thus a high operative mortality is associated with palliative operative procedures for relief of dyspnea and dysphagia Portmann (1941) remarked that, in his series of 220 cases of malignant tumor of the thyroid gland patients dying in the hospital after operation represented 13.0 per cent of all cases Most of the fatalities followed palliation operations decompressions of the trachea because the patients were in a desperate condition Pemberton (1939-1911) recorded a hospital mortality rate of 1.8 per cent in 384 cases of carcinoma of the thyroid subjected to partial thyroidectomy at the Mayo Clinic, the 125 remaining cases in this series underwent other operations including tracheotomy for obstruction, excision of involved cervical lymph nodes and biopsy from the thyroid gland or from metastatic masses and 5 patients died in the hospital (hospital mortality rate, 4 per cent) Obviously earlier diagnosis and treatment would serve to reduce the operative mortality rate as well as to increase the percentage of cures

Results of Operation (With and Without Irradiation Treatment)

In 1939 Pemberton noted that the percentage of patients with malignant lesions of the thyroid gland who had survived for 3, 5, and 10 years after treatment (with or without irradiation therapy) was gratifyingly high — the survival rates after thyroidectomy being 77, 70 and 58 per cent, respectively for the period just mentioned The survival rates among the patients treated by irradiation alone were 29.1, 23.2 and 11.1 per cent respectively Pemberton pointed out that these rates do not indicate cures, they show merely how long the patients survived after treatment A study of survival rates in relation to Broders' histologic method of grading cancer showed that the lower the grade of malignancy, the more favorable the prognosis In Pemberton's series (1939), there were 108 traced patients who had lesions of grade

1 malignancy and who underwent thyroidectomy with or without irradiation therapy, 10 years after operation 80.8 per cent of these patients were alive. Corresponding rates of survival for grades 2, 3, and 4 of malignancy were 62 per cent, 40 per cent and 3.2 per cent, respectively (after 10 years). Pemberton has further observed that Prognosis in carcinoma of the thyroid gland is in inverse proportion to the certainty of clinical diagnosis. Prognosis is most favorable after thyroidectomy and irradiation in papillary adenocarcinoma of grade 1, the malignant nature of which is not suspected clinically; the prognosis is least favorable in diffuse adenocarcinoma of grade 4, the malignant nature of which is diagnosed before operation.

Hare (1941) reported the following 5 year survival rates in 231 cases of carcinoma of the thyroid; the patient's course in each instance having been carefully followed subsequent to surgical and radiation treatment.

FIVE YEAR SURVIVAL RATE IN 231 CASES OF
CARCINOMA OF THE THYROID (Hare 1941)

Type of Lesion	Per Cent
Fetal adenoma	71
Papillary cystadenoma	62
Papillary adenocarcinoma	80
Alveolar adenocarcinoma	27
Small cell carcinoma	22
Giant cell carcinoma	17
Fibrosarcoma (3 cases)	33

Portmann (1941), in his analysis of the results of treatment in 220 cases of malignant tumor of the thyroid gland, classified the cases into four groups: (1) cases without clinical evidence of malignant tumors of the thyroid gland, the neoplasms being small and their malignant nature being revealed only after microscopic examination of tissues removed, (2) cases without clinical evidence of malignancy, or the existence of malignancy suspected only because of the age of the patient and recent rapid enlargement of a goiter of long standing, or malignancy discovered at operation or microscopic examination—the tumor being still localized within the capsule of the gland, (3) cases with clinical or pathological evidences of malignancy, the tumor having invaded or extended beyond the capsule of the gland, no clinical or

roentgenological evidences of metastases being observed, (4) cases with clinical or pathological evidences of malignancy and also evidences of metastases. The survival rates for 5 years were Group 1, 100 per cent, Group 2, 68.0 per cent, Group 3, 23.0 per cent, and Group 4, 3.3 per cent (all methods of treatment, operation followed or not by irradiation treatment and irradiation treatment alone, as palliation). Obviously, again, the extent of involvement influences the results of treatment. In regard to histopathological types as a factor determining the results of surgical treatment (with or without irradiation treatment), Portmann found that, within the 5 year period after treatment, no patient with adenocarcinoma not originating in adenoma died of cancer. Of the patients with papillary carcinoma 70.6 per cent were cancer free after 5 years. Among the patients with malignant adenoma, only 14.3 per cent were alive without cancer after 5 years, but 3.17 per cent were alive or died of cancer after 5 years. More favorable results were obtained in cases of lymphosarcoma. 25 per cent were well and one third lived as long as 5 years (largely because these cases responded well to irradiation). All 4 patients with scirrhus carcinoma and carcinoma sarcoma failed to survive 5 years after surgical and irradiation treatment. No benefits were observed as a result of irradiation of patients with tumors still localized within the capsule of the thyroid. On the other hand, irradiation apparently prolonged the lives of some patients with extensive involvement from malignant tumors of the thyroid gland. Improved techniques of irradiation may be expected to yield better results than those obtained by clinicians employing the older techniques.

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CHAPTER VIII

THYROIDITIS

THYROIDITIS we may define as inflammatory reaction of the thyroid gland to injury, which may be caused by trauma, by local or systemic infectious processes and, perhaps, by some obscure toxic factor or factors. Toxic substances and pathogenic microorganisms are transported to the thyroid by the abundant blood supply of the gland. Yet the thyroid is remarkably resistant to local infection, as shown by the studies of Roger and Garnier as long ago as 1898 and by many subsequent researches. The pathological changes brought about in the thyroid gland by circulating toxins and microorganisms are seldom of such a nature as to be observed clinically. Farrant (1913) carefully investigated and described the effects on the gland caused by toxins in cases of some of the acute infectious diseases. He noted diminution or disappearance of colloid from the follicles, degeneration and desquamation of the lining cells of the follicles, increased vascularity of the gland, and hyperplastic changes in the epithelium. At times the hyperplasia may be remindful of that characteristic of certain stages of primary thyrotoxicosis. Farrant's findings have been confirmed by Cole, Womack, and Gray (1929) and other workers. Womack and Cole (1931) and Womack (1944) have considered thyroiditis in the broadest sense of the term, which then includes inflammatory reaction to physiologic and pathologic states of stress, as when an increase in function is required in the maintenance of homeostasis. Thus, the thyroid gland is a labile organ and responds to increased demands (as for the maintenance of oxygen consumption at a certain level, under conditions of stress) not only by an increase in function but also by demonstrable morphologic alterations in cells and often groups of acini. Hyperfunction may result in residual damage: changes in size and structure of acini, extravasation of colloid into the surrounding stroma, vascular damage, fibrosis and even calcification. In most nodular goiters there are demonstrable degenerative changes that are followed by fibrosis, such processes—representing basic inflammatory

response to injury (often caused simply by physiologic or pathologic stresses) — probably contribute to the development of the nodularity. Nevertheless, thyroiditis, in its *clinical* sense, signifies (1) acute suppurative thyroiditis, (2) acute nonsuppurative thyroiditis, and (3) chronic thyroiditis, Riedel's struma in particular. Until recently, most authorities have included Hashimoto's disease (struma lymphomatosa or lymphanoid goiter) with Riedel's struma — if the two were indeed regarded as distinct entities — under the general heading of chronic degenerative thyroiditis. At present, however, the consensus seems to be that Hashimoto's disease has little in common, basically, with the types of thyroiditis that are apparently the result of inflammation following infection. Hashimoto's disease, we believe, represents a degenerative process whose etiological factors must be assumed to be closely related to physiologic developments in loss of ovarian function (Parmley and Hellwig 1946, see page 263).

Thus beyond the microscopic changes that represent gradual inflammatory reaction to minor stresses throughout the life span, there occasionally occur in the thyroid gland the more conspicuous inflammatory processes in which the gland may swell, become tender and undergo marked alterations in structure and function. In the various acute inflammatory reactions, there may or may not be suppuration, marked constitutional upset, or grave toxemia — depending upon the nature of the thyroiditis, its course, and the treatment employed.

Often a distinction is made between inflammatory reaction in a normal gland and a similar reaction in a goitrous gland, the former type of inflammatory reaction being designated as a thyroiditis and the latter as a strumitis. In a nodular gland, hemorrhage into the stroma of the thyroid induces an inflammatory response, chiefly monocyte in type, the inflammation is most frequently, however, limited to the immediate vicinity of the nodule involved so that only a local tenderness may be noted. Later, however, as an acute or subacute thyroiditis, there may be a prolonged enlargement of an entire lobe. Such lesions are more common in young adults, who may thus for the first time show evidence of the presence of a nodular goiter. Subsequent to resolution of the hemorrhage, the indicated treatment is the same as in any other case of nodular goiter. It is believed that the goitrous gland is far more susceptible to acute inflammatory reaction than is the normal gland.

Trauma may be an indirect rather than a direct cause of an acute thyroiditis, the inflammatory reaction, to become acute, must involve the effects of infection by some microorganism. Infection may be indirect, as when bacteria enter the gland by way of the blood stream or lymph channels, or direct, as when bacteria are introduced into the thyroid by the injury. In the latter case, the source of infection may be through the damaged trachea or esophagus.

ACUTE SUPPURATIVE THYROIDITIS

Although the thyroid gland is remarkably resistant to common infectious processes, pyogenic infections do occasionally occur. Acute suppurative thyroiditis may be associated with a generalized septicemia or may follow an acute infection of the pharynx or respiratory tract. A great variety of organisms have been encountered in this condition (Joll, 1932, Womack, 1944) — almost any type may be present (Womack), including the bacilli of tuberculosis or typhoid fever, the colon bacillus, and innumerable others. The infection may be mixed, a secondary invasion may follow infection by the primary causative organism. It is to be noted, however, that even in cases of extensive miliary tuberculosis, miliary tubercles within the thyroid substance are rarely encountered. Exceptionally, a massive solitary tuberculoma or diffuse tuberculosis may develop, and with such a condition an acute suppuration may be associated. As we might expect, in acute suppurative thyroiditis the organisms most frequently found are the staphylococci and streptococci.

As stated by Kocher (1898), probably most forms of acute thyroiditis are secondary to foci of infection elsewhere in the body. The organisms gain entry to the gland almost invariably by way of the blood stream or lymphatic vessels, in rare instances an acute inflammatory process of the larynx or trachea may extend to the thyroid. Still more rarely, an infection may reach the gland by way of a persistent thyroglossal duct (Meeker, 1925). A nonsuppurative thyroiditis may later give rise to acute suppuration, the borderline between nonsuppurative and suppurative thyroiditis not always being distinct. For instance, at times after pneumonia a minor infection of the thyroid may develop and very slowly progress to the formation of an abscess. Such slowly developing acute suppurative thyroiditis is usually the result of infection by some organism other than the common pyogenic types, although

of course the latter may also gain entry into the substance of the gland and exacerbate the condition. The entire gland may be affected, but more often only one lobe or a portion of one lobe is involved.

Generally, in acute suppurative thyroiditis, the onset is sudden. The gland becomes swollen and tender, presenting the usual picture of inflammation. The temperature invariably rises, and occasionally the patient suffers chills. The outstanding symptom is pain—which may be referred to the mastoid region. The patient complains that swallowing is painful, hoarseness is sometimes a symptom. If the isthmus is involved, the depression in the sternal notch may be filled. There may be eccentric as well as diffuse swelling of the neck when the abscess or abscesses are limited to one lobe or the isthmus. Because of the close relation of the ribbon muscles of the neck, the patient may keep the neck in flexion.

Usually it is possible to palpate the thyroid but the outlines may be quite masked by edema, the extreme tenderness may make examination difficult.

As emphasized by Hertzler (1911), the onset may be so stormy that the systemic reaction to thyroiditis may overshadow the local picture, the lesion may even be overlooked until rupture into the trachea, larynx, or esophagus or through the skin occurs, often with disastrous results. In very rare cases, when virulent organisms are involved, large portions of the gland may slough and be discharged along with the purulent contents, as in gangrene.

In treated cases, rupture into the trachea is rare. In untreated cases the acute infection extends into the deeper spaces of the neck. Myxedema may result from destruction of large portions of the parenchyma. When the condition is diagnosed early, however, and adequate chemotherapy is employed, the infectious process may be reduced to such an extent that abscess formation does not occur. Surgical drainage is indicated in case of abscess and entails adequate exposure of the affected part of the gland, the pathways to the mediastinum must be protected at the same time. The use of the oxygen tent may be necessary to ensure sufficient oxygen intake (Womack).

In early cases, examination discloses an indurated gland with marked subcutaneous edema, and little more. A granular, friable tissue may be obtained by incision. In the acute stage, histological examination reveals dark hemorrhagic foci and pale infarcts scattered through

out the structure of the affected portions which are engorged with blood. When liquefaction occurs, scattered small abscesses may form and then coalesce into large irregular abscess cavities. The pathological changes may involve eventually the entire gland and the suppurative process may extend into the fascial planes of the neck. Microscopic study of sections reveals a connective tissue intensely infiltrated with polynuclear cells and aggregation of leukocytes into definite purulent foci. The causative organism may be seen in large numbers. Remains of exfoliated acinar epithelium may be encountered at some distance from the abscess wall. The epithelial cells are found in various stages of degeneration and usually fill the lumina of the follicles. The colloid may be absent or liquefied and poorly staining. At times we may come upon giant cells of the foreign body type, these are observed around masses of colloid and apparently destroying it. In areas affected to a minor extent by the inflammatory process we may see merely hypertrophy and hyperplasia of the follicular epithelium, as in very mild cases of thyroiditis.

ACUTE NONSUPPURATIVE THYROIDITIS

The symptomatology of acute nonsuppurative thyroiditis resembles that of acute suppurative thyroiditis in general character but not in degree or intensity of the manifestations. In rare cases, the nonsuppurative type may give rise to acute suppurative thyroiditis, such an outcome is more likely in the aged and feeble. Most cases are self limited, however, subsiding usually in from 10 days to 2 weeks.

As compared with acute suppurative thyroiditis, in the nonsuppurative inflammation the onset is not so abrupt and the general manifestations are mild. Fever may be slight or even absent. The thyroid gland enlarges and becomes very tender, but the swelling and tenderness throughout the soft tissues of the neck are not as marked as in the suppurative type. As a rule, the swelling of the thyroid is definitely diffuse, however, and the entire front of the neck appears indurated, but the outlines of the swollen gland are perceptible on palpation. Movement of the neck and swallowing may be decidedly painful. Generally, constitutional symptoms are not conspicuous and may be entirely absent. Differentiation between the acute nonsuppurative and acute suppurative varieties of thyroiditis is not always easy, however, and many borderline cases are encountered in the course of time.

Even a mild onset may feature acute suppurative thyroiditis and diagnosis may be delayed

Satisfactory bacteriologic and morphologic studies are yet to be reported in cases of acute nonsuppurative thyroiditis — in all probability largely because surgical interference is seldom indicated. Approximately 50 per cent of patients give a history of recent upper respiratory tract infection. In many other cases, the lesion may appear in association with any one of a great variety of acute infectious diseases. And, as we have mentioned, the nonsuppurative inflammation may proceed to suppuration and abscess formation in the occasional case. Hence it would seem that we are justified in assuming a bacterial origin for the great majority of cases even though the bacteriological findings have been neither notable nor enlightening. No particular type of organism appears to be etiologically significant, and certainly the familiar pus producing organisms are seldom encountered. On the other hand, not infrequently no microorganism is to be found even after careful microscopic studies and, at the same time, no other infection — local or systemic — may have preceded or accompanied the development of the thyroiditis, at least insofar as can be ascertained.

Pathological examination usually reveals that the inflammation has been confined within the capsule. Nevertheless, the capsule may be involved to such an extent that the gland becomes fixed to the adjacent structures. Edema is marked. Certain resemblances to the leukocytic infiltration characteristic of struma lymphomatosa may be noted, but differentiation is generally attained readily, the lymphadenoid picture is at most scarcely suggested. In still other cases, a true fibrosis may eventuate, dense bundles being distributed throughout the gland, which may thus be divided into fields. The connective tissue may be edematous and stain poorly with acid dyes. Colloid is absent or pale staining and the acinar epithelium may have undergone extensive disarrangement and degeneration. Interspersing the areas of fibrosis, polynuclear infiltration and early or late acinar degeneration there are areas of normal or approximately normal parenchyma.

One source of confusion in diagnosis may be encountered the acute inflammation may give rise to constitutional symptoms suggesting hyperthyroidism. The erroneous diagnosis of toxic goiter may be suggested — and has occasionally been made.

Destruction of the parenchyma may proceed — though exception

ally — to the point at which symptoms of myxedema appear. Prolonged inflammation may result in abscess formation. Suppuration may be insidious and pus may accumulate for weeks or longer before the true condition is evident.

RIEDEL'S STRUMA (STRUMA FIBROSA)

Attention was first directed to ligneous or woody thyroiditis as a specific entity by Riedel (1896, 1897, 1910). Riedel stressed the iron hardness of the tumor, its firm attachments to contiguous structures, and, as the most prominent feature of the lesion, the dense infiltration with connective tissue. Riedel further remarked that the condition, at least in the first few cases observed by him, occurred with about the same frequency among the 2 sexes, commonly during the fourth decade of life, although it may appear in younger or older individuals. In 1904, De Quervain described what he regarded as a more acute and granulomatous form of chronic thyroiditis, the giant cell variant of Riedel's struma. In 1912, Hashimoto reported his observations on struma lymphomatosa, which he distinguished from Riedel's struma because of the characteristic replacement of the glandular structures by lymphoid tissue, the firmness rather than bony hardness of struma lymphomatosa, its comparatively slight adherence to contiguous structures, and its occurrence almost exclusively among females. For almost 3 decades after these early reports there was a conflict of observation and opinion concerning the nature and etiology of the forms of chronic thyroiditis described by Riedel, De Quervain, and Hashimoto. The studies of Graham (1931), Clute et al. (1935), McClintock and Wright (1937), Joll (1939), Harry (1940), McSwain and Moore (1943), and Schilling (1945) have served practically to establish the clinical and pathological distinctions between Riedel's struma and Hashimoto's disease as separate entities. De Quervain and Giordanengo (1936), Crotti (1938), and Schilling (1945) recognize a granulomatous, giant cell variant of struma fibrosa (Riedel's struma). The etiology of Hashimoto's disease remains quite obscure (Bothe, 1944; Womack, 1944; Schilling, 1945; Parmley and Hellwig, 1946). As regards the etiology of Riedel's struma, we have recently advanced a new theory (DeCourcy, 1942, 1943), that this disease is a result of a previous perithyroiditis which causes a partial constriction of the vessels entering the gland. This theory is based upon extensive evidence, and, a.

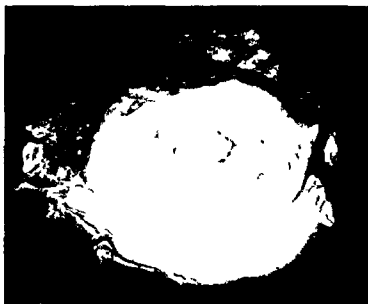


Fig. 15 Chronic nonspecific thyroiditis (Riedel's struma) The mass is white very hard enclosing in the center some but slightly affected thyroid tissue The surface of the mass shows extraglandular tissue it was necessary to remove (From Hertzler A E *Surgical Pathology of the Thyroid Gland* Philadelphia 1936 J B Lippincott Co)

noted by Schilling (1915) in his comprehensive review of the known facts in support of our conclusions would seem to explain in satisfactory terms the hitherto obscure nature of the causative influences leading to the development of Riedel's struma The evidence supporting our conclusions will be discussed in detail in a later section (page 251)

Clinical Features As a disease of the thyroid Riedel's struma is of relatively rare occurrence In the DeCourcy Clinic the condition has been encountered in about 2 per cent of all thyroidectomies, hence its incidence appears to be approximately the same as that of cancer of the thyroid Riedel found that both sexes are about equally affected and other observers are in general agreement, Schilling (1915) stated that between 60 and 80 per cent of patients suffering from Riedel's struma are females

In the early stages toxic symptoms may be entirely absent and the basal metabolic rate may be normal Evidence of hypofunction may exceptionally be present (Womack 1911), although in other cases



Fig. 4C Chronic nonspecific thyroiditis (Reidel's struma). Only parts of the mass could be removed. The mass at the right x has attached an overlying muscle. (From Hertzler, A. E. *Surgical Pathology of the Thyroid Gland*. Philadelphia, 1936. J. B. Lippincott Co.)

there may be a slight elevation of the basal metabolic rate (possibly to be ascribed to the patient's psychic reaction to the onset of symptoms). As a result of the connective tissue infiltration, involvement of adjacent structures by the fibroblasts, and gradual enlargement of the gland, symptoms of obstruction sooner or later appear. Thus there may be compression of the trachea, esophagus, larynx, and blood vessels, and pressure may be exerted upon neighboring nerves. Edema resulting from compression of the jugular veins and dysphagia caused by pressure on the esophagus are usually seen earlier than severe tracheal obstruction leading to dyspnea. Respiratory difficulty may also be

caused by tracheal displacement in cases in which only one lobe is involved (30 per cent of cases) The early feeling of pressure is usually followed or accompanied by hoarseness, stridor, or even aphonia because of the involvement of the laryngeal nerves, although such symptoms are relatively rare Commonly the disease involves first one lobe and then the other, in about 70 per cent of cases the entire gland is found to be enlarged when the patient is first seen As fibrosis becomes more pronounced, the tumor assumes a bony hardness (iron hardness) Evidence of extraglandular fibrosis—fixation of the gland and some loss of distinctness of outline—may appear in the early stages, such findings are characteristic of the later stages

From a review of the literature, one would judge that the onset of Riedel's struma is not acute Lee (1935) described its onset as insidious, Fox and Missal (1911) stated that the average duration of symptoms is about 7 months, and Schilling (1945) believed the duration of symptoms to be between 1 and 2 years (but, in the case of the giant cell variant of struma fibrosa, between and 1 and 12 months) The duration of symptoms, however, may be much less During the past few years at the DeCourcy Clinic we have operated* upon two patients with Riedel's struma who entered the hospital acutely ill and remained for surgery, these cases will be described in detail in a later section page 255)

Differential Diagnosis Although admittedly difficult, the diagnosis of woody thyroiditis usually can be made prior to operation by the characteristic consistency of the gland and by a normal, slightly subnormal or mildly elevated basal metabolic rate—thus differentiation from diffuse toxic goiter may readily be achieved Carcinoma of the thyroid gland should be considered The firmness of the tumor suggests carcinoma, but the extreme hardness, the absence of nodules, and the more or less indefinite borders of the glandular enlargement aid in differentiation Also, carcinoma usually develops in the presence of a pre-existing goiter

In Riedel's disease, when the temperature is elevated, the fever may be expected to subside rapidly The tendency is toward fibrous formation rather than suppuration Hence differentiation from acute suppurative thyroiditis is possible

In contradistinction to Riedel's struma, Hashimoto's disease occurs

* As of April 1 1948 we have operated 15 such cases

almost invariably in women and usually at a somewhat later period of life (ages 40 to 60), the thyroid gland undergoes bilateral enlargement characteristically and does not become as hard as in woody thyroiditis. The onset is more insidious in struma lymphomatosa and the pressure symptoms are, as a rule, less marked, the tendency toward fixation of the thyroid gland is less evident.

Pathologic Features *Gross Appearance* The thyroid gland in Riedel's struma is glistening white, smoothly enlarged, very hard, and characteristically densely adherent to contiguous soft tissues, the pretracheal muscles being involved also. The avascularity of the gland is a highly significant feature and is receiving increasing attention in relation to our theory of the etiological factors involved in the development of the struma, as will be pointed out later. In general, the gland may be described as avascular except where overgrowth of fibrous tissue has served to maintain the patulousness of a large vessel. The enlarged gland is typically so densely adherent in true struma fibrosa that it may be cut only with the greatest difficulty and resection may be physically impossible unless we employ continuous sharp dissection without identity of adjacent structures, vessels or nerves. In some cases, removal of the isthmus to free the trachea may be all that can be safely accomplished unless only a portion of the gland is involved. If the entire gland and surrounding soft structures are involved resection, and at times merely subtotal resection, may be excessively difficult and dangerous.

Unless a lobe is uninvolved, it is to be emphasized, not only is extreme avascularity an obvious feature but also the adhesive characteristics are highly conspicuous. In approximately 30 per cent of the cases, the process — when encountered first — has not extended beyond one lobe, such cases may be regarded as in early stages of the disease or as in a stage at which the disease process has been retarded, held back from its characteristic progress. In many cases, the esophagus may be completely surrounded. At times, the fibrous enlargement of a lobe may encapsulate and compress a colloid adenoma. We have emphasized the frequently obvious evidences of a perithyroiditis in which a thickening of the capsule and an induration of the surrounding tissues are observed (DeCourcy, 1942, 1943).

Histopathologic Features Microscopic examination of Riedel's struma reveals strikingly dense fibrous tissue invasion. Such epithelial

elements as may remain are, in the typical case, compressed by the fibrous overgrowth. The acinar epithelium may be entirely absent in involved areas of the gland, in other areas the acini may be nearly normal in appearance but may vary in size, shape and colloid content. The epithelial cells are frequently normal cuboidal with centrally located nuclei. Commonly we observe many acute and chronic inflammatory cells which have infiltrated the connective tissue planes, the presence and number of such cells vary according to the stage of the disease and the area examined. These infiltrating cells are less numerous in advanced stages of the process.

Lymphocytes, wandering monocytes, and plasma cells are encountered in varying numbers, and in the earlier stages pseudogiant cells or perhaps even true giant cells may be seen. Various observers have reported frequent giant cell reaction, the giant cells at times presenting bizarre appearances because of the resemblance of the colloid to the cytoplasm of the cells. Goetsch (1940) expressed the belief that the giant cells are composed of a syncytium of degenerating thyroid cells, are not phagocytic, and represent evidence of the degenerative process associated with inflammatory reaction. Certainly degeneration of the thyroid cells and the colloid is detectable or obvious in a high percentage of cases. De Quervain (1936) and Schilling (1945) have insisted that in the giant cell variant of struma fibrosa the distinguishing features are cellular aggregates resembling foreign body giant cells, acute degeneration of the acini, and a granulomatous appearance. These authors have noted further, as have many other recent authors, that whether or not one recognizes the existence of a giant cell variant of struma fibrosa, an outstanding histological feature of Riedel's struma is the thickening of the intima and media of the arterioles. Moreover, the vessels are surrounded by a cuff of fibrosis in most instances. These characteristic vascular involvements are intimately concerned in our explanation of the causative factors underlying the development of Riedel's struma.

Theories of Etiology. The etiology of Riedel's struma, or ligneous thyroiditis, has received the attention of numerous authors. Many theories have been proposed, some of which have been discarded, whereas others still have their adherents. Specific organisms have not been noted consistently in fibrous thyroiditis. It is generally conceded that syphilis and tuberculosis are not involved as causative factors.

Actinomyces, streptococci, and numerous other organisms have been considered speculatively but no important evidence of direct and constant etiological significance of any specific form has been forthcoming. Many authorities, however, still regard it as possible that different organisms may play an etiological part in the development of the disease under different conditions by directly causing or by participating in a basic inflammatory reaction.

The oldest theory concerning the causation of Riedel's struma is that the condition is a result of a local inflammatory process in the thyroid gland, and a number of prominent contemporary authorities have favored this view (Graham, 1931, Harry, 1940). Graham's observations and conclusions in 1931 were of the utmost importance in establishing the now generally accepted conception of Riedel's struma and Hashimoto's disease as distinct entities, thus the unitarian belief of Ewing (1922) — that Riedel's struma is a sequel to struma lymphomatosa — has been overshadowed. Ewing termed Riedel's struma benign granuloma of the thyroid and suggested that it might represent a precancerous condition. Graham, in his consideration of the etiology of Riedel's struma, pointed out that in this disease the general body economy is affected only secondarily as a result of the degeneration of thyroid tissue, the interference with deglutition and respiration, and injuries to the important blood vessels and nerves. Such a process, Graham noted, has its counterpart in other organs and tissues, which may be expected to respond in a similar manner except for the fact that the thyroid gland is so situated as to render more likely the development of complications.

Much the same view was expressed more recently by Harry. In discussing the pathogenesis of struma fibrosa, he emphasized the evidence which suggests that the process represents chronic inflammatory reaction. To support this suggestion, Harry cited such factors as the early stimulation of the gland function, subsequent destruction of the parenchyma, extensive fibrosis, the presence of cells typically encountered in chronic inflammatory states and the existence of similar lesions in the adjacent cervical tissues.

McKnight (1936) remarked that we are prone to neglect the existence of inflammatory reactions other than those caused by bacterial invasion. It was his suggestion that the pathologic picture of Riedel's thyroiditis results from the action of some obscure biochemical irritant.

differing from that produced in or causing exophthalmic goiter Zelle and his associates (1939), in describing a case of Riedel's struma in a 33 year old woman, expressed the belief that the disease is caused by abnormal response of the thyroid to physiologic demands. Similar beliefs have been set forth by some other writers.

Conversely, a number of workers have opposed the theory that the disease is inflammatory in nature. It has been variously suggested that the condition may result from adrenal dysfunction, or from over stimulation by thyrotropic hormone of the pituitary, or from the degeneration of a previously enlarged thyroid. These and other ideas concerning possible etiological factors have been discussed recently by Bothe (1944), Womack (1944), Schilling (1945), and Parmley and Hellwig (1946), who have pointed out that there is no convincing evidence to support any of these theories. As Schilling has concluded etiological theories based upon the conception of the prime significance of inflammatory reaction have the greatest weight of evidence in their favor at the present time.

Role of Perithyroiditis. The literature just reviewed would seem to indicate that the consensus pictures the involvement of the capsule of the thyroid gland in Riedel's struma as the result of fibrosis arising within the tissue of the gland and extending outward so that eventually the process comprehends tissue beyond the capsule and surrounding it. It is our opinion, however, that the primary etiological factor in Riedel's struma is a perithyroiditis, i.e., we believe that the fibrous process begins outside the gland rather than inside the thyroid itself.

That this perithyroiditis is always associated with Riedel's struma in younger persons is demonstrated by the close adherence of the overlying muscles to the gland. Now is this associated perithyroiditis a secondary result of the disease itself or is it the basic etiologic factor?

It has always been our belief that Riedel's struma is a vascular rather than a glandular disease and that it begins with a perithyroiditis which produces secondary changes within the gland itself. The findings of Goldblatt and his associates (1940) in regard to the secondary effects of renal ischemia are decidedly pertinent. In their extensive studies on experimental hypertension, Goldblatt clearly demonstrated the profound effect of partial occlusion of the renal blood vessels on specific organs and tissues. Not only did thickening of the intima and media of the blood vessels result but also fibrous whorls developed about

these vessels, these pathological changes in the blood vessels are quite similar to those typically occurring in Riedel's struma

A perithyroiditis with the adherent muscles would certainly cause some constriction of the thyroid vessels and their superficial tributaries and a condition of partial ischemia would obviously result. Consequently, we would expect a secondary fibrosis to result, as in Riedel's disease. The compression of the smaller vessels and the comparative avascularity of the cut surface of the hard fixed tumor in Riedel's disease have been stressed as conspicuous features of the condition by many observers (Hertzler, 1942, Schilling, 1945). Large vessels may be held to some degree patulous by the induration. The tendency toward fibrous reaction in ischemic conditions has been observed not only in the kidneys of experimental animals but also in surviving human thyroid glands in organ culture, necessarily under partially ischemic conditions, the problem of adequate blood supply being practically insurmountable.

Harry (1940) remarked the variation in the condition of the blood vessels in different specimens of Riedel's struma and observed that pronounced thickening of the arterioles and small arteries is the rule although in some instances these vessels may appear normal. Harry noted further that the number of capillaries is reduced. In different cases, we may point out, perithyroiditis would be expected to cause different degrees of compression and partial ischemia and, therefore different degrees of thickening of blood vessels (as in the varying response of the renal blood vessels and renal tissue to varying degrees of partial ischemia, as noted by Goldblatt).

Two recent case histories from the DeCourcy Clinic may serve to clarify the discussion of our theory of the etiology of struma fibrosa.

CASE 1 — V. P., a 42 year old married, white female, entered the clinic on Nov. 8, 1941, because of loss of weight and nervousness. She presented a history of sore throat, which had occurred 1 month previously, but no history of goiter. Her temperature was 102 degrees F., blood count, 17,800 white cells per c.c., differential, polymorphonuclears 73 per cent, small lymphocytes, 25 per cent, eosinophiles, 1 per cent, basophiles 1 per cent. Lung fields and heart were normal. Wasserman and Kahn tests were negative.

Her thyroid was symmetrically enlarged, each lobe being about 3 times normal size. Her neck overlying the gland was exquisitely tender, with no evidence of external inflammation.

She was referred back to her family physician who kept an icebag on her neck and ordered her to remain in bed. Sulfathiazole, 10 gr was given every 4 hours for 4 days. Because of the persistence of her symptoms, however, she was admitted to the Good Samaritan Hospital on Nov. 14, 1941.

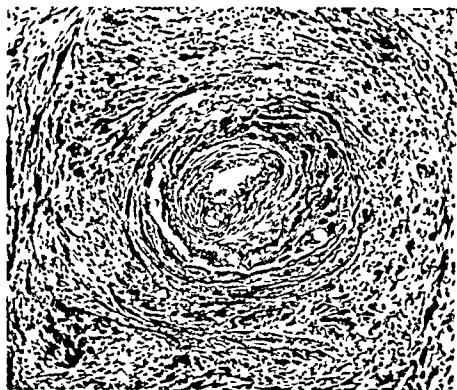


Fig. 17. A small artery showing hypertrophy of media with reduction of lumen and surrounding collar of dense hyalinized connective tissue (Hortega silver impregnation stain)

While she was in the hospital, her temperature range was between 98 and 102 degrees F. Her pulse was 88, respiration 22, blood pressure 138/78, basal metabolic rate (two readings), plus 16. No medication was given during this time except Lugol's solution. In 5 days she returned to normal but the thyroid remained enlarged and hard, although the tenderness had disappeared.

Bilateral subtotal thyroidectomy was performed on Nov. 21, 1941.

When the excised gland was examined grossly, the appearance was definitely that of Riedel's struma. The organ was white and muscle fibers in large numbers had densely adhered high over the side of the lobes, which had to be removed by sharp dissection. There was very

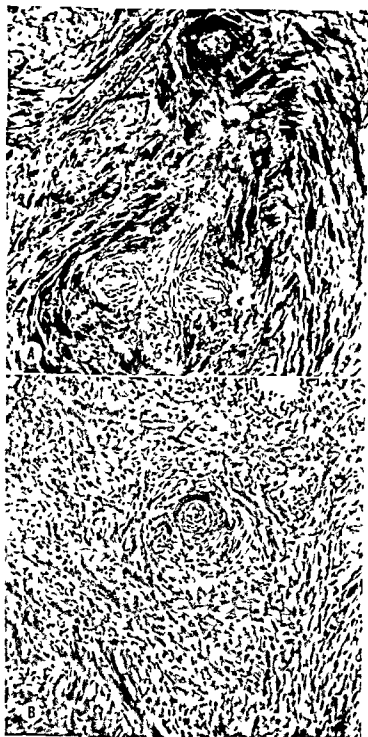


Fig 48A and B A small artery showing medial hypertrophy and a precapillary arteriole showing sclerosis obliteration and surrounding collar of dense hyalinized connective tissue, marked hyalinization of the entire stroma (Hortega silver gold impregnation stain)



Fig 19A and B Photomicrograph showing sclerosed arterioles and obliteration of thyroid acini by fibrous tissue (Hortega double silver gold impregnation stain)

little bleeding from the cut surfaces. The outer portion of the lobe was most involved and thyroid tissue could be seen beginning about 1 cm from the capsule. The colloid, however, appeared to have a whitish color rather than the red color usually seen.

Dr. William Germaine, pathologist to the Good Samaritan Hospital, reported the following microscopic findings: There was compensatory hyperplasia, intense fibrosis, marked strangulation of functioning thyroid elements, marked arteriosclerosis, formation of pseudo-granulomata and pseudogiant cells. The diagnosis was Riedel's struma.

The postoperative period was uneventful. Her temperature reached normal on the fourth postoperative day and remained afebrile to the time of her dismissal.

She has since regained her normal weight, and is taking desiccated thyroid, 1 gr. daily, 1 month after her operation.

CASE 2 — E.K., a 59-year-old single, white female, entered the Clinic on Sept. 10, 1941. Four weeks prior to admission she had become aware of increasing nervousness, loss of weight, tachycardia, and at

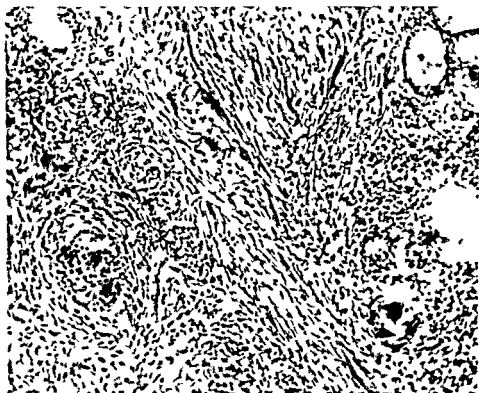


Fig. 50 (x 160) Riedel's Struma. Fibrosis, pseudogranulomata, pseudogiant cells.

times, a choking sensation in her throat. At the time of admission, her temperature was 99 degrees F, pulse, 88, respiration, 22; blood pressure, 168/90, basal metabolic rate, plus 20. Her thyroid was diffusely enlarged, about 2½ times normal size, and was quite tender to touch. There was no evidence of external inflammation.

No history of previous goiter could be obtained, although the patient thought that her neck had appeared to be somewhat swollen during the past 4 years. It had not been as hard as at present. Her blood picture was as follows: hemoglobin, 86 per cent, red blood cells, 4,280,000, white blood cells, 12,800, differential count: polymorphonuclears, 76 per cent, small lymphocytes, 23 per cent, basophiles, 1 per cent. The remainder of the physical examination was essentially negative except for a fine tremor of the hand.

A diagnosis of woody thyroiditis was made, and Lugol's solution, 10 drops, 3 times daily, was given.

A subtotal thyroidectomy was performed on Sept. 8, 1911.

The gross pathological findings in this instance were essentially similar to those found in the previous case. Whitish appearance of the gland, adherent muscles, etc.

The microscopic examination was reported by Dr. William Germaine as follows: There is replacement of thyroid by diffuse struma fibrosa in which there is extensive strangulation of gland-bearing tissue, advanced fibrosis, islands of lymphoid tissue, and formation of pseudo-granulomata and pseudogiant cells. There is also a marked arteriolar sclerosis.

Diagnosis: Riedel's struma.

Forty-eight hours after operation, the patient's temperature became normal and remained so to the time of dismissal on the fifth post-operative day.

These cases are interesting primarily because of their acute onset which was evidently associated with a perithyroiditis, and because of the tenderness of the overlying structures, the elevated temperature which subsided rapidly, and the lack of any tendency to suppuration. The possibility exists that these febrile periods were merely the result of exacerbations of an already existing condition, the same finding, however, has frequently been reported by other writers. It is our belief that, had these patients not been operated upon, probably the cases would have been classified as acute nonsuppurating thyroiditis. Possibly several years would have elapsed before surgery was undertaken and a definite diagnosis made.

It is pertinent that Hertzler, in discussing Riedel's struma, stated

that whatever the disease may be, it is neither a true inflammation nor a true tumor. Considering the clinical and pathologic findings, we might say that these cases represented acute nonsuppurating thyroiditis which became chronic. If this is a true expression of what occurred, then it must be concluded that it is possible for acute nonsuppurative thyroiditis to metamorphose quickly into chronic nonsuppurative thyroiditis or Riedel's disease. Notable evidence in support of this conclusion has been recorded by De Quervain and Giordanengo (1936). They studied 8 cases of subacute and chronic thyroiditis of a non-specific etiology and were able to trace clearly the various stages from acute to subacute to chronic thyroiditis. De Quervain and Giordanengo held that struma fibrosa is a later phase of an acute thyroiditis, which may be followed by progressive pathologic changes.

Considered grossly, cases such as the 2 which we have cited cannot be mistaken if seen early, it is possible however, that perithyroiditis has been mistaken for acute nonsuppurative thyroiditis.

We were fortunate in obtaining sections from the first case, which we consider to be representative of a very early stage of the disease. In this instance, the surrounding glandular tissue was involved, while recognizable thyroid tissue still remained in the interior of the gland. Thus it appears that the spread of the fibrous tissue and the extension of the pathologic process as a whole take place from without and proceed inward—rather than that the process originates within the gland and progresses by extension outward toward the periphery and beyond.

These findings represent evidence distinctly favoring our theory that a perithyroiditis is primarily responsible for the woody consistency of the gland and that this fibrous formation does not result from a process originating within the gland itself. Further, although a few cases of Riedel's struma have been reported as occurring in association with a pre-existing goiter, we have never encountered such a case in our experience. Schilling (1945) stated that Riedel's struma does not arise in association with a goiter.

Perithyroiditis appears to have been a neglected topic in medical literature. We have been unable to find any mention of the condition even in standard treatises and yet, when operating for goiter, the surgeon not infrequently encounters evidence of perithyroiditis. It has been the experience of most surgeons that it often becomes necessary

to use sharp dissection in freeing nodular goiters from their beds. This experience, we believe, cannot be accounted for unless we assume that a perithyroiditis previously existed. At present we seem to be encountering such cases with increasing frequency, the explanation remaining obscure.

The suddenly induced tendency toward involution subsequent to the administration of iodine in nodular goiter may cause this apparent fixation, no important evidence, however, has been forthcoming in favor of such an explanation. Boyden, Collier and Bugher (1935) suggested that iodine administration may be the chief etiological factor in Riedel's struma. Zelle and his collaborators (1939) remarked in regard to this theory. It also seems to us that Riedel's struma was observed before Lugol's solution was used for goiter therapy. In the case reported by Zelle et al. the patient had received the drug in only small quantities and during a very brief period. Likewise, in the 2 cases just cited by ourselves, treatment with Lugol's solution was neither prolonged nor in large dosage, far more significantly, however, in both instances the condition involved an acute inflammatory reaction which was well advanced before the administration of the drug.

Another consideration is that the spectacular involution which follows the use of iodine in diffuse hyperplastic goiter is not induced in nodular toxic goiter. In these cases, there is the conceivable possibility that the iodine does not penetrate to the glandular tissue because of the dense capsular thickening and therefore a chemical perithyroiditis (lymphangitis) may be produced in the surrounding tissues. In all probability, however, the blood supply is sufficient to transport the iodine in quantity to the parenchyma.

In summary, we may state that, in common with the majority of workers, we regard Riedel's struma as a condition resulting from an inflammatory reaction. Nevertheless, we have proposed the new theory that the inflammatory reaction within the thyroid gland is secondary to a partial ischemia resulting from a previous perithyroiditis, which must be looked upon as the primary etiological factor in the development of fibrosis within the gland. The pathologic process in Riedel's struma thus is pictured as beginning outside the capsule of the gland and as proceeding inward. The perithyroiditis brings about a constriction of the thyroid vessels and associated blood channels. The fibrous overgrowth within the gland is an inflammatory response to the resultant

ischemia. A review of the pathology of Riedel's struma and the clinical features of the disease has provided considerable evidence indicating just such an etiology. Finally, in our opinion, this conception of the causation of struma fibrosa has not previously been advanced because the consideration of perithyroiditis as a not uncommon condition has been neglected.

HASHIMOTO'S DISEASE (STRUMA LYMPHOMATOSA)

In Hashimoto's disease, the glandular tissue of the entire thyroid is gradually replaced by lymphoid overgrowth, or diffuse interacinar lymphocytic infiltration which gives rise to numerous lymph follicles with germinal centers. Fairly uniform enlargement of both lobes and the isthmus is characteristic. The gland is resilient, firm rather than hard (as in Riedel's struma) and nodular. Usually there is little adherence to surrounding structures beyond some slight attachment to the trachea. Vascularity is normal or slightly decreased. The surface of the gland is smooth and often yellow although the color varies from white to brown, because of the lymphoid overgrowth and moderate fibrosis the cut surface has a trabeculated meaty appearance. A preoperative impression of adenomatous goiter may at times be given by the lobulated appearance produced by the fibrous trabeculae. Fibrosis however, is not present to the extent characteristic of Riedel's struma. Microscopic examination reveals lymphoid follicles of various sizes often large with enormous germinal centers the alveoli are atrophic and compressed by the lymphocytic infiltration. Characteristically there is little colloid. The acinar epithelium is generally dull, granular and cuboidal. The germinal centers may show mitotic figures.

The clinical picture associated with Hashimoto's disease is vague rather than distinctive. With very few exceptions the reported cases have occurred among women—and generally in the fifth or sixth decade of life. Neither hyperthyroidism nor hypothyroidism is characteristic in early cases. Occasionally, hypothyroidism may develop but almost always in mild form. The failure of severe or advanced myxedema to develop may be accounted for by the slowness of the process in this disease and by some compensatory hyperplasia of persistent glandular structures. In late stages of thyroiditis, however such hyperplasia may not be adequate to maintain a metabolism within the normal range, and clinical myxedema may supervene. (Thyroidectomy in



Fig. 51 Lymph nodule with germinal center in early chronic lymphatic thyroiditis (a) follicles surrounded by lymphatic infiltration (b) Lymph follicle with germinal center (c) Acini obliterated by the infiltration the cells of which are palely staining (from Hertzler, A. E. *Surgical Pathology of the Thyroid Gland* Philadelphia 1936 J. B. Lippincott Co.)

cases of Hashimoto's disease frequently leads to myxedema.) The mild compressive symptoms that may be anticipated are not infrequently encountered. At times, there is a slight relative lymphocytosis. In some cases, it may be possible to make a clinical diagnosis on the basis of clinical and gross findings, a preoperative diagnosis when hyperthyroidism is present may be extremely difficult. In most reported cases, the diagnosis has depended chiefly on the findings of the pathologist.

Not all contemporary authors recognize Hashimoto's disease as an entity distinct from Riedel's struma (Ewing, 1922, Williamson and Pearce, 1929, Eisen, 1931, Womack, 1944). The consensus, however, is that 2 lesions represent different pathological pictures and present different clinical symptoms (Hashimoto, 1912, Graham and McCullagh, 1931, J. G. Lee, 1935, McClintock and Wright, 1937, C. M. Lee and McGrath, 1937, Joll, 1939, Moore and Lloyd, 1942, McSwain and Moore, 1943).

In 1912, Hashimoto reported 1 case of thyroiditis in which the glandular structures were to a large extent replaced by lymphoid tissue

He stressed the involvement of the whole gland, the very slight adherence to contiguous structures (the trachea excepted), the absence of obstructive symptoms, the tendency toward postoperative hoarseness, and a lengthy convalescence. He called attention to the fact that all his (four) cases occurred in older women. Further, Hashimoto noted infiltration with connective tissue, but, above all, he emphasized the extreme abundance of lymphocytes, diffuse and in the form of lymphoid follicles of varying sizes with germinal centers—hence his term, *struma lymphomatosa*. This type of lesion he considered an entity distinct from Riedel's *struma* both clinically and pathologically.

In contrast, Riedel (1896) in his original papers recorded five cases of thyroiditis in which the iron hardness of the tumor suggested a malignant lesion. At operation the gland was found to be attached to the trachea, the carotid artery and the internal jugular vein. Riedel reported that, upon microscopic examination he observed both spindle cells and round cells, but, as is disclosed by inspection of his drawings the most prominent feature of the lesion is the dense infiltration with connective tissue. Lymph follicles are absent and lymphoid cells are present in small numbers only. In the first 5 cases recorded by Riedel there were 3 males and 2 females.

Four cases of thyroiditis were studied by Ewing (1922), who stated that the pathological changes described by Riedel in *Eisenharte Struma* and by Hashimoto in *struma lymphomatosa* could be found simultaneously in the same thyroid. Ewing expressed the belief that the extreme degree of fibrosis in Riedel's *struma* represents the end result of the changes observed in Hashimoto's disease. This hypothesis leads to the conclusion that both types of lesions are caused by the same underlying pathological disturbance and are not 2 distinct clinical entities but simply early and late manifestations of a single process.

Ewing's suggestions have been supported and extended by a number of later authors. Williamson and Pearse (1929) evolved the conception that the thyroid has a lymphogenic function which may, when perverted, lead to the accumulation of lymphoid tissue, as in the condition described by Hashimoto. They applied the term *lymphadenoid goiter* to this type of thyroiditis and regarded the fibrosis as a creeping replacement of injured reticuloendothelium, the end result being—as in the process suggested by Ewing—the condition first described by Riedel, Riedel's *struma*.

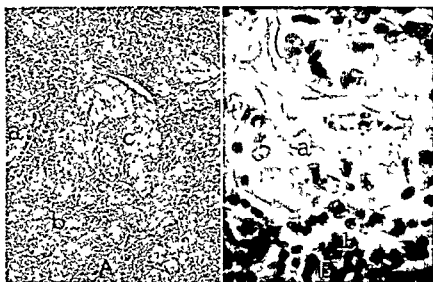


Fig 52 Chronic lymphatic thyroiditis (A) Low power (a) edge of lymph follicle, (b) intense lymph cell infiltration (c) acini filled with large foamy cells (B) High power (a) large ill staining cells sometimes mistaken for metastases of adrenal tumors, (b) lymph cells (From Hertzler, A E *Surgical Pathology of the Thyroid Gland* Philadelphia 1936, J B Lippincott Co)

Graham and McCullagh (1931), after reviewing the cases reported by Hashimoto and almost all cases subsequently recorded, presented their own observations on a struma lymphomatosa, these authors were able to give impressive support to the belief that Hashimoto's disease and Riedel's struma are two quite distinct types of thyroiditis. They again emphasized the gross and microscopic distinctions noted by Hashimoto, further, they pointed out the lack of evidence to the effect that the diffuse lymphoid infiltration of Hashimoto's disease is followed by productive fibrosis and scar tissue formation in such degree as to bring about the development of the condition characteristic of Riedel's struma. Of 104 cases of struma lymphomatosa collected by Graham, 95.8 per cent were women, the average age at which the symptoms were first observed was 52.1 years. The comparatively advanced age at which the onset of symptoms was noted must be regarded as evidence against the view that Riedel's struma is a sequel to Hashimoto's disease.

Joll (1939) carefully studied a series of 51 cases of his own in which the diagnosis was Hashimoto's disease, to this series he was able

to add 30 cases the data on which were communicated to him by other workers Joll's observations convinced him that Hashimoto's disease and Riedel's struma are definitely separate entities both clinically and pathologically Like Graham, he stressed the point that in Riedel's struma a diffuse lymphocytic infiltration does not occur, although an occasional lymph follicle may be found Concerning the incidence of struma lymphomatosa, Joll reported 51 cases in 5,650 thyroidectomies (i e, slightly less than 1 per cent)

In 1943, McSwain and Moore summarized the findings in 71 collected cases of Hashimoto's disease, they noted that the average age at which these patients presented themselves for treatment was 47 years, the majority (39 cases) first seeking treatment between the ages of 41 and 60 years In one case, however, the patient (female) was only 14 years old, at the other extreme was a patient aged 75 years Sixty eight of these cases were female, and 3 were male These authors also found that in reports on 11,049 operations on the thyroid, the incidence of struma lymphomatosa was 1 in 116, or slightly less than 1 per cent



Fig 53A and B Chronic lymphatic thyroiditis (A) Intense lymphatic infiltration all but obliterating the acini (B) Acini in which the epithelium is exfoliated into a cavity devoid of demonstrable colloid The exfoliated epithelium is in a state of degeneration (From Hertzler, A E *Surgical Pathology of the Thyroid Gland*, Philadelphia, 1936, J B Lippincott Co)

In general their analysis of the 71 collected cases provided evidence decidedly favoring the views of Graham and of Joll

Womack in his recent review (1944) of the prolonged controversy regarding the relationship of Hashimoto's struma lymphomatosa to Riedel's struma stated that there seems to be a definite difference in the clinical picture in isolated well defined types of the two conditions Further according to Womack It seems apparent from a consideration of the microscopic appearance of the 2 lesions that they present a quantitative rather than a qualitative difference and the syndromes that ensue are related to the predominance of a particular type of inflammatory reaction in Riedel's goiter it is fibrosis in Hashimoto's type it is lymphoid overgrowth Often both have been noted in almost equal amounts and this has led to discussions as to classification that have not been too illuminating Nevertheless Womack remarked It has been assumed by some that the fibrosis is an end stage of a lymphadenoid type but evidence to support this very logical assumption is not too apparent It is his contention that the 2 lesions represent parallel manifestations of the same underlying injury Womack in discussing the possible causative factor or factors underlying the 2 conditions laid considerable emphasis upon the finding that identical changes in the thyroid are encountered in adrenal cortical insufficiency It must be observed however that (1) there is no satisfactory evidence in favor of the view that any considerable number of patients with chronic thyroiditis (Riedel's struma or struma lymphomatosa) suffer from adrenal cortical insufficiency (2) few patients with adrenal cortical insufficiency have an associated thyroiditis (3) in many cases postmortem examination of the thyroid glands of patients dying of adrenal cortical insufficiency has revealed no changes comparable to those characteristic either of Riedel's struma or Hashimoto's disease Moreover neither the lymphocytes nor the structure of the lymph follicles in Hashimoto's disease have been shown to differ from those encountered less extensively in exophthalmic goiter status thymolymphaticus or (still less extensively) in Riedel's struma

Attempts to show that some microorganism (bacterium rickettsia or virus) is consistently present as an etiological agent in cases of Riedel's struma or struma lymphomatosa have ended only in failure McCarrison (1929) reported that he was able to produce lymphadenoid goiter in rats by a deficient diet confirmation however has

not been forthcoming. The influence of iodine administration has been frequently considered as a possible etiological factor, but few authorities at present believe that iodide therapy plays any part in the development of either type of lesion (McSwain and Moore, 1943). Obscure physiologic or metabolic factors have been suggested as significant by various authors, but in no instance has the relationship of any such factor to Hashimoto's disease or Riedel's struma been established. Graham has expressed the belief that struma lymphomatosa may be an early stage in the development of a subsequent lymphosarcoma. Still, the etiology of Hashimoto's struma remains quite obscure.

As regards the etiology of Riedel's struma, our view is that this condition is a vascular rather than a glandular disease, the changes progressing from outside the gland rather than from within the organ itself (DeCourcy, 1942 see page 247). That is, Riedel's struma is believed to begin with a perithyroiditis which induces constriction of the thyroid vessels and associated blood channels. The tissues of the thyroid respond to this ischemia by the formation of the ligneous tissue characteristic of Riedel's struma.

Further, in our opinion, it is clearly conceivable that Riedel's struma should develop as an entity distinct from struma lymphomatosa (as in the consensus at present, of course) — but may so develop in the same patient (as has not been suggested, to our knowledge) — before or after, or even simultaneously with, the latter disease. It is indeed universally recognized that the presence of one disease in any organ does not necessarily preclude the concurrent or intercurrent development of a second (or even a third or fourth) disease. For instance, in the thyroid itself, carcinoma and myxedema (or, in other cases, exophthalmic goiter) may coexist, 1 disease arising before or simultaneously with the other, yet quite independently. In such manifestations of confused pathologies, we believe, is to be found the explanation of the hitherto confusing picture of associated extensive fibrosis and extensive lymphocytic infiltration. In Riedel's struma, the predominant inflammatory reaction is fibrosis, in Hashimoto's disease, it is lymphoid overgrowth — yet, in many confusing cases, both types of inflammatory reaction have been encountered in varying degrees or even apparently equal amounts. It may be logically pointed out that such confusing findings — which have led to still endless discussions on classification — do not provide evidence against our views concerning the etiology of Riedel's

struma Riedel's struma arises as a distinct entity — quite independent of struma lymphomatosa, yet the former may develop at any time within the same thyroid in which the latter may occur. The relative amounts of fibrosis and lymphoid infiltration have frequently been reported to vary conspicuously from case to case, whether the diagnosis was Riedel's struma or struma lymphomatosa. Such observations have been the source of most of the confusion in classifying various types of thyroiditis.

In exceptional instances, the conception of independent origins must be modified in a very minor manner, as follows. A perithyroiditis may be produced as a result of a developing struma lymphomatosa. Hence in possibly rare cases it may be true that an ischemia produced by Hashimoto's disease can give rise to Riedel's struma. Again, however, such a possibility is comprehended by our conception of the mode of origin of Riedel's struma.

In view of the occurrence of struma lymphomatosa almost exclusively among females near the time of the menopause, it would seem the better part of wisdom to withhold further speculation regarding the etiological factors involved. It may be that the genesis of the condition is as obscure as — and possibly related to — the profound physiological phenomena whose interaction and reaction result in the manifestation, hyperthyroidism. Certainly, hyperthyroidism is a disease which affects women in the ratio of about six to one (the ratio, of course, depending upon the locality) as compared to the incidence in men. Hyperthyroidism becomes more frequent at the menopause — and is characterized by some degree of lymphocytic infiltration. Of course, slightly subnormal metabolism is characteristic of struma lymphomatosa — but, as Marine has well expressed the pliability of the gland, extremes meet in the thyroid. Indeed hyperthyroidism may be associated — exceptionally — with struma lymphomatosa (Womack, 1944). And, as far as concerns gonadotropic and female sex hormones as possible causative factors in this condition, we must not forget Graham's belief that the condition of struma lymphomatosa is a stage in the development of a lymphosarcoma. Indeed in view of the known complexity of endocrine interrelationships, it would seem unsafe to rule out the hypothesis that the adrenal cortical hormones (particularly in their deficiency) may be somehow related to the origin of Hashimoto's disease.

The literature discloses that extirpation of the gland has been the treatment of choice in cases of struma lymphomatosa. Nevertheless, the frequently adverse results definitely indicate further consideration of the problem of optimal control, myxedema not uncommonly follows subtotal thyroidectomy in this condition. Also, following thyroidectomy, hoarseness is present for many months. Renton et al (1938) have recommended radiation — when a diagnosis could be established, they have reported good results. It is our belief that surgery is especially indicated when the diagnosis is established and obstructive symptoms are obvious.

McClintock and Wright (1937) and Scarcello and Goodale (1941) have recorded cases in which no significant change in the microscopic picture was observable after 2 years and 13 years, respectively, when microscopic studies were possible, in struma lymphomatosa. Just such determinations, in our opinion, suggest the difficulties in the way of future research that would seek to solve the intricate problem of Hashimoto's disease forthwith.

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CHAPTER IX

EXOPHTHALMIC GOITER (DIFFUSE TOXIC GOITER)

CAUSATION OF SIGNS AND SYMPTOMS

THERE seems to be a widespread tendency nowadays to base diagnosis on the presence of certain characteristic symptoms giving scant attention to the reasons underlying their existence. This practice is well exemplified in the case of exophthalmic goiter.

When a patient who is losing weight in spite of a good appetite is found to have a rapid pulse, protruding eyeballs, a tremor in the fingers and an enlargement in the neck, the average physician concludes. He has the 4 cardinal symptoms. He must have exophthalmic goiter. But, often as not, he does not give a thought to the why and the wherefore of these symptoms.

Very few of us ever stop to think of the underlying reason for the exophthalmos, tachycardia, tremor or enlargement in the neck, to the explanation for the benefit from Lugol's solution, or to the principles controlling the choice between medical and surgical treatment. Many of these questions of course are unanswerable in the present state of our knowledge. But that is all the more reason why we should give serious thought to their solution.

The new pages of medicine have not all been written by laboratory research workers. There is still abundant room for careful clinical observations based on exact anatomic and physiologic knowledge. And exophthalmic goiter is peculiarly a disease adapted to clinical observation, inviting all studious physicians to investigate the reasons underlying its complex symptomatology.

ROLE OF INVOLUNTARY NERVOUS SYSTEM

It has been known for years that the clinical signs of exophthalmic goiter closely approximate the phenomena produced by stimulation of the inferior cervical sympathetic ganglia. Recently the close relation

between the involuntary nervous system and the symptoms of exophthalmic goiter has been substantiated by the work of Hyman and Kessel. These investigators have emphasized the fact that the symptoms of exophthalmic goiter are identical with those produced in normal individuals by substances having a strong affinity for the sympathetic nervous system, such as epinephrine.

Hyman and Kessel believe that the involuntary nervous system may produce the manifestations of exophthalmic goiter through the action of some unknown circulating sympathomimetic toxin. Such substances, however, have not as yet been isolated, although epinephrine is capable of producing these effects. Another possibility is the loss of some restraining influence, such as that of the hormones of the parathyroid glands or the suprarenal cortex.

According to an old theory it was held that the symptoms of exophthalmic goiter are due to thyroid oversecretion. In this connection it is known that feeding with very large quantities of thyroid extract may occasionally produce an incomplete picture of exophthalmic goiter. As hyperplasia of the thyroid gland occurs regularly in cases of exophthalmic goiter, it would seem logical to attribute the disturbance to thyroid hypersecretion. Furthermore, the fact that myxedema, which is alleged to be the antithesis of Basedow's disease, is recognized to be due to a hyposecretion of the thyroid gland and that the symptoms of exophthalmic goiter are relieved by subtotal thyroidectomy would seem at first thought to point to an important relation between the quantity of thyroid secretion and the existence of the disease.

Nevertheless, the view that the symptoms of Basedow's disease are due entirely to thyroid hypersecretion is untenable. In the first place, they can be brought on only by doses exceeding the secretory capacity of the gland, and two of them — exophthalmos and glandular hyperplasia — cannot be produced by even very large doses. Secondly, the hyperplasia is not associated with any increase in the output of the thyroid hormone, in fact, the actual storage of this substance is diminished. Thirdly, the symptoms of myxedema and exophthalmic goiter may coexist, showing that the two diseases are not truly antithetic. Finally, it is not permissible to ascribe all of the benefit of subtotal thyroidectomy to the operation itself, as much of it is undoubtedly due to the rest before and after operation.

The most likely explanation for the pathogenesis of exophthalmic

goiter is that the condition is dependent on a disturbance of the sympathetic nervous system influenced by various sympathomimetic agents such as infection psychic upset and some obscure thyrogenic factor. This hypothesis is entirely consistent with our ability to produce the symptoms of exophthalmic goiter by stimulating the inferior cervical ganglia.

Chauffard and Girod assert that the first phase of exophthalmic goiter is a change in the thyroid gland with subsequent hyperthyroidism and that the second phase is a hyperepinephrinemia from an exaggerated secretion of the suprarenal glands. This view would support Cannon's theory of the synergistic action of the thyroid and suprarenal glands.

THE OCULAR SIGNS

Exophthalmos. Years ago Claude Bernard produced protrusion of the eyeballs experimentally by electric stimulation of the cervical sympathetic. The orbitalis muscle which is supplied by this chain of nerves is stretched across the sphenoidal fissure at the apex of the orbital cavity. Contraction of this muscle following sympathetic stimulation pushes the capsule of Tenon and its contents forward thus causing exophthalmos.

Another factor in the production of exophthalmos is a sustained contraction of the levator palpebrae superioris muscle which draws back the upper lid so as to expose the sclera. This action is brought about by the contraction of the Mullerian muscle fibers in the lid which are under sympathetic control.

Thyroid overfeeding cannot produce exophthalmos. However Maurice was able to show a direct relation between this condition and overactivity of the suprarenal capsules. The conclusion seems well founded that protrusion of the eyeballs results from the response of the unbalanced involuntary nervous system to some sympathomimetic substance.

Signs of Von Graefe, Stellwag and Moebius. Von Graefe's sign is a failure of the upper lid to follow or a lagging behind when the eyeballs are directed downward. The result is that a margin of white sclera above the pupil is exposed and there is a widening of the palpebral fissure. Stellwag's sign refers to the infrequency of blinking in exo-



Fig 54 Primary thyrotoxicosis The smoothness of the gland is well shown Exophthalmos is a striking feature (From Joll C A *Diseases of the Thyroid Gland* London Wm Heinemann Medical Books Ltd)

phthalmic goiter, Moebius sign to a weakness in the convergence of the eyeballs, as elicited by attempts at fixation on the finger held nearby

All of these ocular signs may be produced experimentally by stimulation of Muller's muscle also called the tarsal muscle This muscle consists of a thin sheet of involuntary muscle fibers found in the vicinity of the convex borders of the tarsal plates In the upper lids the fibers intermingle with those of the levator palpebrae superioris their function, therefore is to retract the eyelid The Mullerian muscles however, are supplied by sympathetic fibers derived from the cervical sympathetic chain, whereas, the levator palpebrae superioris is innervated

by the antagonistic autonomic system through the oculomotor nerve

It is entirely reasonable to suppose that not only the exophthalmos but also the Von Graefe, Stellwag and Moebius signs are caused by the action of some sympathomimetic substance like epinephrine on an oversensitive sympathetic nervous system

THE CAUSE OF TACHYCARDIA

A pulse rate consistently above ninety and subject to marked acceleration following slight exercise or psychic influences is one of the characteristic features of Basedow's disease

The tachycardia does not arise from an oversecretion of thyroid hormone, as was at one time supposed. Marine and Lenhart, after extensive histologic studies on thyroid glands in exophthalmic goiter, came to the conclusion that the differences in pulse rate under normal conditions and in cases of colloid and of exophthalmic goiter are so slight as to suggest no causal relation. Kendall has shown that there is no tachycardia after the administration of thyroid substance. If, however, amino acids are injected at the same time, the pulse rate is greatly increased.

The accelerator nerves of the heart, whose function is directly antagonistic to that of the vagi, arise from the cervical sympathetic ganglia. It has long been known through physiologic experimentation that stimulation of these nerves or the ganglia from which they arise produces marked acceleration of the pulse, or conversely that section of them slows the heart rate to a pronounced degree.

The attacks of tachycardia in exophthalmic goiter are associated with the subjective symptoms of sympathicotonia, as described by Eppinger and Hess. The patient is conscious of his heart beat, describing it as palpitation, he feels as if his heart were up in his throat, he reacts with a state of nervous excitement and anxiety, and the functions of the gastro intestinal canal are inhibited.

Most authorities hold that the tachycardia of Basedow's disease results from stimulation of the cardio accelerator centers in the cervical sympathetic ganglia by some sympathomimetic substance having an action similar to that of epinephrine. Thus considered, it is apparent that both the cardiac and ocular symptoms may well arise from the same or closely related sources.

Cardiac disorders developing during the course of exophthalmic

goiter are of frequent occurrence. They have generally been attributed to tachycardia and overstimulation. However, Boas has called attention to two hitherto neglected factors as largely responsible for the cardiopathy of Basedow's disease.

In the first place, the tremendous dilatation of the vessels of the thyroid gland short circuits the blood flowing to the neck and thus increases the load on the heart in the same manner as an arteriovenous aneurysm. Secondly, the heightened oxygen consumption produces an increased minute volume flow of the blood, which may be 25 to 60 per cent greater than normal. In Boas' opinion, the increased work thus thrown on the heart is the principal cause for cardiac dilatation, hypertrophy and decompensation in exophthalmic goiter.

WHY THE BASAL METABOLIC RATE IS INCREASED

One of the most essential findings in toxic cases of exophthalmic goiter is an increase in the basal metabolic rate. This explains why individuals with this disease may have excellent appetites and nevertheless lose weight.

An important factor in accounting for the increased metabolic rate is the increased aeration in the lungs. A greater supply of oxygen naturally increases oxidation and the height of caloric consumption.

We have long known that epinephrine relieves asthmatic seizures by relaxing the involuntary musculature of the lungs and bronchi. This result is accomplished by sympathetic stimulation. Thus the sympathetic nerves of the respiratory system, when stimulated, greatly increase the breathing capacity and may in this way account in large measure for the increased basal metabolic rate.

It must be admitted that an increased secretion of thyroid hormone may directly heighten the basal metabolism. This factor probably plays a part in some cases. However, as the output of thyroxin may be normal or diminished in toxic cases of exophthalmic goiter, we cannot attribute the metabolic change solely to the thyroid hormone.

As is well known, very high basal metabolic readings, amounting to as much as 50 to 90 per cent above normal, may be obtained in cases of exophthalmic goiter with toxic effects. Feinblatt and Eggerth have pointed out that there is usually a direct proportion between the basal metabolic and the basal pulse rate. This, in itself, would indicate that these two symptoms have a common origin.

ORIGIN OF THE TREMOR

A fine rapid tremor, best observed in the outstretched and separated fingers, is one of the cardinal symptoms of exophthalmic goiter. In severe cases, this tremor may affect all the muscles of the body.

At first thought it may seem difficult to explain a tremor in voluntary muscle on the basis of sympathetic stimulation. But Langley has shown that all voluntary muscles have a definite sympathetic nerve supply. In fact, tonus in voluntary muscles is largely the result of a steady influx of stimuli through the sympathetic fibers in the peripheral nerves and the gray and white rami of the spinal roots, whereas voluntary movements result from impulses descending through the medullated fibers. Thus considered, the tremor of exophthalmic goiter is really a disturbance of muscle tonus, resulting from overstimulation of the sympathetic innervation. And again we revert to the common cause for the symptoms of exophthalmic goiter, namely, stimulation of the sympathetic nervous system by some unknown circulating sympathomimetic toxin.

VASOMOTOR SYMPTOMS

Vasomotor symptoms, especially of the face, are common in exophthalmic goiter. Such patients flush on slight excitement and a throbbing of the arteries of the head and neck is sometimes observed. Examining the fundus oculi one frequently detects a distinct pulsation of the branches of the arteria centralis retinae. Another common vasomotor symptom is profuse sweating, usually on the face, it may be unilateral or bilateral.

The vasomotor symptoms obviously arise from sympathetic irritation. They may be reproduced experimentally by stimulating the cervical sympathetic nerves. Vasomotor symptoms in the extremities have a closely associated origin, as has been shown by Scott.

GASTRO INTESTINAL SYMPTOMS

Reference has already been made to the most pronounced alimentary symptoms of exophthalmic goiter, namely, progressive loss of weight in spite of an excellent appetite. This condition, as has been pointed out, is a direct result of the increased basal metabolism.

The most striking symptoms directly referable to the digestive tract

are vomiting and diarrhea. However, they usually occur only late in the disease and are probably secondary to disturbance of the vasomotor centers.

The flow of saliva may be increased, more rarely there is dryness of the mouth. The increased flow of saliva results from an overactivity of the nerves supplying the salivary glands. Ordinarily the acidity of the gastric juice is reduced.

SYMPTOMS REFERABLE TO THE THYROID GLAND

Enlargement of the thyroid gland is the rule in exophthalmic goiter, although this condition is not invariably present. Pathologic examinations have shown that the enlargement is due to hyperplasia of all the elements of the glandular structure but that the storage of colloid material, iodine and thyroxin is actually diminished.

The bruit heard over the thyroid gland in cases of exophthalmic goiter may be accounted for by the close proximity of the goiter to the common carotid artery. Since the goiter presses upon the vessel so as to narrow its lumen, the mechanical conditions are such as to favor the production of a murmur, that is, the blood rushing through the narrowed lumen suddenly pours into the wider vessel beyond the limits of the goiter, thus giving rise to the eddying currents which cause the murmur.

The consistency of the enlarged gland is an important factor determining the presence or absence of a bruit. Adenomatous glands, being freely movable, ride upon the carotid artery without constricting it, therefore, no bruit is produced. The hyperplastic gland of exophthalmic goiter, on the other hand, is fixed and necessarily constricts the artery. These pathologic conditions account for the frequency of a bruit over the thyroid gland in cases of exophthalmic goiter and its infrequency in cases of adenomatous goiter. It has been observed that, as the consistency of the goiter is diminished by the administration of Lugol's solution, the bruit gradually disappears.

It is interesting to note that filaments of the sympathetic nerves encircle the inferior thyroid arteries. If, for any reason, there is an increase in the diameter of these vessels, irritation of the cervical sympathetic ganglia may result from this source. This irritation may, in turn, stimulate the heart. The increased force of the heart beat then increases the diameter of the inferior thyroid arteries still further,

thus again increasing the tug on the sympathetic nerves and setting up a vicious circle (McClintock)

Considering all the available evidence, we must give great weight to the view that most, if not all, the symptoms of exophthalmic goiter result from irritation of the sympathetic nerves. These symptoms may be produced experimentally by sympathetic stimulation. And it appears probable that an instability of the sympathetic nervous system, in conjunction with the presence of some unknown sympathomimetic toxin, may explain the complex symptomatology of Basedow's disease.

As Lieb, Hyman and Kessel have demonstrated,¹ autonomic imbalance presents all the symptoms of exophthalmic goiter with the single exception of the increased basal metabolic rate. Furthermore, the majority of patients give a history past or present, of autonomic imbalance and the actual transition from autonomic imbalance to exophthalmic goiter has been observed.

The underlying cause of the disturbance of the sympathetic nervous system and the nature of the sympathomimetic toxin are still unknown. The disorder may be initiated by emotional states, such as fright, worry or shock, by systemic infections or localized foci, particularly focal infection in the rhinopharyngeal tract, by toxemias of any kind, by too quick a return to normal activities after debilitating diseases, such as influenza, by faulty diet, by pressure on the cervical sympathetic nerves from an enlarged colloid or adenomatous goiter, or by various other causes.

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CHAPTER X

THE THYROID GLAND IN LATER LIFE

AS THE GENERAL population has aged during the past several decades we have encountered increasing numbers of patients in the higher age groups and all aspects of geriatrics have been brought into prominence as never before in the history of medical science. Not only the clinical problems involved in the treatment of the older patient but also the fundamental problems of gerontology, the science of senescence, are now attracting vastly increased attention and rightly so. As is well known the endocrine glands — because of their profound influences upon physiology and even morphology throughout the life span — have inspired more extensive investigations than have any other organs in the research upon the factors involved in the processes of normal and pathological aging. Many investigators have been particularly interested in the relationship of the thyroid gland to senescence and the onset of senility, as pointed out by Carlson (1912), Bruger and Rosenkrantz (1912), Hertzler (1912) and Goldzieher (1916). A number of authorities have noted the striking similarities between the picture of old age and that of marked hypofunction of the thyroid gland — reduced metabolic rate, lack of vigor, dry and scanty hair, dry skin of lowered vitality, sensitivity to cold and diminished mental initiative and capacity. Hertzler (1912) has stated categorically: "A man is as old as the colloid in his thyroid gland." He also expressed the belief that, in advanced years the thyroid gland is obviously incapable of performing its normal function and therefore follows the thymus into retirement. Apparently because of the secretion of some undetermined toxic factor, according to Hertzler, it may be that in later life the thyroid hastens the onset of cardiac difficulties and other features of senility. In this connection it is interesting to note that Vogeler (1929), in an isolated study which does not seem to have been followed up, adopted as his criterion of the activity of the thyroid the minimum quantity of dried powdered gland which would bring about transformation of tadpoles. Vogeler thus obtained evidence of a slight increase in the activity of the thyroid in old men as compared

to the activity of the gland in middle age, in old women there was apparently no decrease or detectable increase in the activity of the gland as determined by this method. Carlson (1942) has summarized, at considerable length, the evidence for and against the view that the thyroid gland is involved as a basic factor in the aging process. In his fascinating discussion of the problem, Carlson reached no definite conclusion and stressed the need for more research; he did remark, however, that, in any consideration of the nature and causes of senescence, the influence of the thyroid gland must be regarded as of fundamental importance. Certainly, we would like to emphasize, dysfunction of the gland—whether hypofunction or hyperfunction—markedly promotes the onset of senility. And the characteristic changes in the physiology and histology of the thyroid during the latter part of the life span involve problems of the profoundest nature in gerontology.

It is true that, whereas evidence of hypofunction of the thyroid gland has been reported in instances of precocious senility, rarely has any amelioration of the symptoms of senility resulted from thyroid medication—and then, presumably, only when there was definite hypothyroidism. In such instances, however, we must remember that another factor is probably concerned—general tissue reaction to hormonal influence. When dysfunction of the thyroid has existed for any considerable length of time, as the years pass the capacity of the aging tissues to respond to thyroid hormone must change. Further, in the later years of life the vital reserves of the body have markedly diminished and it may be decidedly inadvisable to attempt to stimulate metabolism by thyroid medication. In hypothyroidism of advanced years there has been a decrease in the mass movement of the blood—a slower heart action has eventuated, along with absence of peripheral dilatation and a decreased stroke volume of the heart. Any stimulation may be overstimulation. Experience with geriatric patients has indicated, according to Goldzieher, The decreased activity of thyroid and consequent hypometabolism of the aged rank high among the protective devices of nature. Still, we must not forget that the development of hypothyroidism has not been shown to be a definite and necessary phase of the process of aging. Carlson has spoken of the reserves of functional capacity in the thyroid gland, even in old age. Moreover, hyperthyroidism is frequently encountered in elderly patients—and would be more often diagnosed correctly if it were

not masked by common degenerative disorders of advanced life. The life long influences of the thyroid gland and especially of its periods of hypofunction and hyperfunction must be recognized as undetermined, and, probably, for a long time undeterminable.

CHANGES IN LATER LIFE

Clerc (1912) noted the following changes in the thyroid glands of persons past 50 years of age: degeneration of epithelial cells (with fat and pigment present in them), a concentration or solidification of the colloid, variable increase in the connective tissue within the gland. Cooper (1925) studied the histology of the human endocrine organs at various ages and found that in older individuals the thyroid gland is reduced in size, the follicles and cells are smaller, the colloid is less dense than in youth and may be absent, and the amount of connective tissue is increased. Hinton (1931) studied the thyroid glands of 80 individuals dying from accidental causes, their ages ranged from a few hours (newborn) to 89 years, but there were only 2 cases in which the age was greater than 60 years. This investigator was impressed by the variability of the changes in the gland as age increased, and remarked: "So far we have been unable to draw conclusions as to what is normal thyroid tissue for different ages." In 1933, Dogliotti and Nizzi Nuti examined the thyroid glands of 53 individuals, 9 of whom were 70 years of age or older. These workers also noted that in later life the follicles are smaller and that there is a decrease in the quantity of colloid, but they believed that there was an increase in the volume of the epithelial cells, with an associated increase in the content of granules. Dogliotti and Nizzi Nuti concluded that in old age there is actually an increase in the activity of the thyroid gland. In 1935, these investigators reported further studies of the aging thyroid gland, in 50 aged subjects, they observed no marked increase in the connective tissue of the gland in individuals past middle life and expressed the belief that regressive and degenerative changes generally regarded as characteristic of senescent glands are to be found in thyroids at any age, provided the cause of death has been a severe infection or exhausting disease. In the opinion of Dogliotti and Nizzi Nuti, in old age there is a compensatory hyperfunction of the thyroid gland, as indicated by evidences of epithelial proliferation and a sparse content of colloid within the follicles in many of their specimens.

Allara (1934), likewise studying human material, detected a coarsening of the reticular fibrils and evidence of some transformation of reticulum into collagen in the thyroid gland as age advances. Such changes are, of course, characteristic of senescence in other organs and tissues of the body. Allara found a marked increase in elastic tissue in the capsule and septa of the thyroid but no increase in the collagenous fibers, the cellularity of the stroma was greatly diminished.

In 1938, Rice expressed the belief that definite criteria for ascertaining the normal condition of the thyroid gland at any age can be established, he emphasized the increase in interfollicular connective tissue and in interfollicular groups of epithelial cells. Nolan (1938) analyzed the results of 725 autopsies and observed that, as age increases, fibrosis of the thyroid is more frequently encountered, also with increasing age, there is a decrease in the percentage of normal thyroid glands at a given age.

Garau (1938) reported epithelial hypertrophy and a very thin colloid to be commonly observable in the thyroid gland of aged individuals, and, like Dogliotti and Nizzi Nuti, reached the conclusion that these findings are evidences of compensatory hyperfunction, this increased activity, in his opinion, resulted from degeneration of the follicles in the portions of the gland in which there was an overgrowth of connective tissue. Ghigi and Reggiani (1939) found varying degrees of increase in connective tissue and an increase in the interacinar masses of epithelial cells, thus confirming the findings of a number of other workers. Furthermore, according to Ghigi and Reggiani, in later life there is a tendency toward a stabilized condition of the thyroid gland, which then has numerous large follicles with colloide statica and a lining of squamous epithelium.

In 1939 and 1942, Hertzler summarized the results of his studies on the thyroid gland in advanced years. He regarded the following changes as characteristic and also frankly regressive: an increase in the basophilic properties of the colloid, abortive attempts of the follicles to reproduce, and increase in connective tissue. He noted that the firmer consistency and whiter color of the capsule of the gland in advanced age are evidences of sclerosis which are disclosed by gross inspection. Histological examination of sections reveals fibrotic areas, with distinct fibrous bands. Hertzler stressed the significance of the presence of hyaloid connective tissue — not merely indicative of

advancing years but suggesting more than an orderly retreat. In fact, according to Hertzler, the overgrowth of connective tissue may compress many acini and obliterate their lumen so that the picture of a carcinoma is simulated at certain sites within the gland. This authority made the important point that the increase in the connective tissue may be a secondary, replacement process the primary change taking place in the acini, the notable degeneration of the acini may be evidence favoring such a view. (This consideration has been discussed at some length more recently by Lansing and Wolfe (1944) in their report on the senescence of the thyroid gland in female rats.) Hertzler believed that the flat and irregular cells of the great majority of acini are obviously inactive and in certain areas are altogether defective. Certain other areas within the senescent or senile gland present cells which are remindful of those found in Hashimoto's disease, the cytoplasm being granular or, at times foamy. According to Hertzler, those areas which suggest compensatory hyperplasia may actually represent a pathological development of thyroid tissue whose general effects on the body are decidedly toxic. But it is the colloid whose changes are most significant in old age, Hertzler reiterated. Its basophilic staining properties, vacuolization, granulation and shrinkage are indicative of loss of acinar function and general degeneration of the gland. It is of great interest to note that Hertzler concluded. There is no other organ of the body which shows such early and extensive degenerative changes as does the thyroid gland.

Korenchevsky (1942), in his review of the natural relative hypoplasia of organs and the process of aging recorded the findings supporting the view that the thyroid gland and the heart, in contrast with all other organs of the body exhibit a characteristic increase in size as age increases up to the age of seventy when a decrease in size sets in. It may be, however that a significant percentage of goitrous or otherwise abnormal thyroid glands were included in the studies upon which Korenchevsky based his conclusions. It would seem that further investigation will be required to establish whether or not there is an actual increase in the size of the *normal* gland up to the age of seventy years.

Recent studies on animals have tended to confirm many of the gerontological findings made in researches on human thyroid glands. Thus according to Andrew and Andrew (1942) in senility there is a

definitely regressive process, a true histological involution, of the thyroid gland, the connective tissue increases greatly, often to such an extent that the follicles may appear to be merely islands in proliferating fibrous material. Andrew and Andrew agreed with Garau that interacinar collections of epithelial cells in the senile gland represent degenerate follicles, which are no longer capable of secretion and have been forced into mere clumps of cells by the overgrowth of connective tissue. These workers also found distinct evidences of degenerating colloid—very thin, fluid, poorly staining colloid in many follicles, very solid appearing colloid in other follicles, and split or vacuolated colloid in still others. Andrew and Andrew regarded these findings as indicative of a more static condition of the gland, secretion being overbalanced by reabsorption, both processes proceeding less rapidly than in young glands.

Lansing and Wolfe (1944) observed a coarsening of the reticular fibrils separating the epithelium from the capillaries and an increase in the number of these fibrils, the interfollicular connective tissue likewise becomes coarser and thicker. These workers found, further, that, with advancing age the size of the follicles increases, the epithelium becomes flattened and the staining reaction of the colloid shifts from gray to rose, when silver impregnation technique is employed.

Goldzieher (1946) remarked that such changes as diminished size of the thyroid gland in advanced age, a decrease in the number of cells as well as their size, increase of connective tissue and thickening of the collagenous fibrils (i.e., sclerosis of the stroma) are typical of senescence in all organs of the body. Also, the assumption is justified that, while the cells decrease in size, their function simultaneously descends to a lower level.

HYPOMETABOLISM IN LATER LIFE

The basal heat production tends to decrease in human beings after the age of forty years (Benedict, 1935, Boothby and Sandiford, 1922, Lewis, 1938, DuBois, 1937), and authorities generally have attributed this decrease in basal metabolic rate to the involutionary changes in the thyroid gland in later life which have been recorded by Clerc, Cooper, McCarrison, Hertzler and other workers. As Carlson (1942) and Bruger and Rosenkrantz (1942) have stated, undoubtedly other factors than decreased activity of the thyroid gland play roles in this

decreased heat production Bruger and Rosenkrantz have attempted to correlate the advent of arteriosclerosis with decreased activity of the thyroid gland, and found that the incidence of hypometabolism in subjects 55 years of age or older is greater for those exhibiting arteriosclerosis than for those without arteriosclerotic manifestations. Considerable evidence indicating some relationship between reduced activity of the thyroid gland and the development of atherosclerosis has been forthcoming from observations on animals. Anitschkow (1913) showed that the feeding of diets high in cholesterol will frequently result in the development of atherosclerosis of the aorta in rabbits. This finding has been repeatedly confirmed and the degree of atherosclerosis so produced has been found in general to correspond to the elevation in blood cholesterol. In man, atherosclerosis is not seldom encountered in diabetes mellitus, nephrosis, lipoid granulomatosis, hypercholesteremic xanthomatosis, and myxedema, hence there would seem to be some relationship between hypercholesteremia in human beings and this vascular lesion although extensive studies have not served to clarify the problem. Some antagonism has been found to exist between the thyroid gland and the susceptibility of the vascular tree to lipoid infiltration. Potassium iodide, thyroid substance or thyroxin administration inhibit the development of atherosclerosis in animals fed diets high in cholesterol (Liebig, 1931, 1934, Seel and Creuzberg, 1931, Turner, 1933, Page, 1935). Although a hypofunctioning thyroid gland may promote the deposition of cholesterol in the walls of the blood vessels, as Bruger and Rosenkrantz have remarked, the arterial disease may be primary and be the cause rather than the effect of a diminution in activity of the thyroid. Bruger and Rosenkrantz used the basal metabolic rate as an index of the functional capacity of the thyroid gland in their subjects, but this decrease in basal metabolic rate has not yet been definitely proved to result from decreased activity of the gland. Diminished food intake or the eating of certain diets modifies or impairs thyroid function (McCarrison, 1925, Marine et al., 1925), in fact, studies along this line first disclosed the value of thiouracil and other goitrogenic substances in the treatment of certain types of hyperthyroidism.

For the present at least, we may with apparent logic assume that not only is the reduction in thyroid activity a general though by no means universal manifestation of advanced age, but also this slowing

down of activity is an intrinsic feature of senescence rather than merely one of the sequelae of the processes of aging. Furthermore, the evidence already at hand would seem to be sufficient to indicate some basic relationship between thyroid activity and the onset of atherosclerosis and arteriosclerosis, whatever the primary factors in the relationship. And so, after a review of present knowledge regarding these problems — as little as this knowledge indeed is — we may state confidently that future research will bring to light phases of thyroid activity which are of the first moment not only to gerontology but to the clinical practice of geriatrics. Degeneration of the thyroid contributes substantially to the progressive ravages of advanced age, all the tissues of the body being affected because of their dependence upon the stimulation of thyroid hormone — of this fact we can be sure while awaiting the outcome of present and future investigations.

HYPOTHYROIDISM IN THE ELDERLY PATIENT

The reduction of the basal metabolic rate in elderly individuals may in certain instances be great enough to suggest marked hypofunction of the thyroid gland. In addition, the skin may be dry, the mentation sluggish, and bradycardia may be present. Nevertheless, the therapeutic use of thyroid substance will almost always be found to be contraindicated in such cases. The effects of stimulation of oxygen consumption, metabolism and general tissue activity must be carefully considered. The elderly patient usually has greatly diminished vital reserves, the complete economy of the body has been markedly altered from the condition of youth. Cardiovascular disease is frequently advanced, the patient with a failing heart and arteriosclerosis would not be expected to fare well when stimulated by administration of thyroid substance. In the aged, not just one but several of the common degenerative diseases of the higher decades of life may have insidiously developed. Under such conditions, treatment of hyperthyroidism may be decidedly inadvisable.

HYPERTHYROIDISM IN THE AGED

In recent years, increasing attention has been given to hyperthyroidism in the older individual, and it is now widely recognized that the condition is not infrequent among the elderly. The diagnosis may be missed because of the earlier teaching that toxic goiter is a disease of

the young and the middle aged, and the clinician may not at first consider the possibility. More important, however, is the fact that the symptoms of hyperthyroidism in the older patient are often different from those encountered in the young. The hyperthyroidism may be of the 'apathetic' type, with the basal metabolic rate showing only a slight or seemingly insignificant elevation, in some elderly patients with masked hyperthyroidism, the basal metabolism may be quite within the normal range. The older patient with hyperthyroidism is frequently not stimulated to the degree that a younger patient usually is. This may be the result of aging of the peripheral tissues, or the result of prolonged stimulation of the tissues by the hyperactive thyroid, or other factors even more obscure may be involved. The presence of degenerative disease in the elderly patient not seldom masks the hyperthyroidism, and, conversely, the expectation of finding other conditions than hyperthyroidism may lead to erroneous diagnosis of heart trouble, gastro intestinal malignancy, senile psychosis, Parkinsonism, and neurocirculatory asthenia.

The sex incidence of Graves' disease in individuals past 50 years of age has been found to differ markedly from the sex incidence of the condition in a group of younger patients. Mora and Greene (1931), in a study of 200 cases of thyrotoxicosis in individuals 50 years of age and older, found that the ratio of male patients to females was 2.5 to 1. Bram (1938) reported that, in his series of 322 cases of patients past 50, the sex incidence was approximately 2 to 1, in his experience, the sex incidence of Graves' disease in young adults had been approximately 5 to 1, and in children about 20 to 1. It would seem that the older the patients the closer the approach to parity of sex incidence. In the male, the syndrome appears to develop a decade or more later than in the female. In the series of Mora and Greene, 65.5 per cent of the patients with thyrotoxicosis had diffuse hyperplastic goiters and the remainder had nodular goiters. These clinicians stated that, on the average, 14.5 years had intervened between the development of the goiter and the appearance of symptoms. Crile (1938) reported that as a rule in patients more than 70 years of age the goiter is adenomatous. Bram found that the duration of symptoms as stated by patients past 50 years of age was much greater than in the younger patient, further, the average patient more than 50 years old presented evidence of circulatory insult indicative of years of suffering. It also seems to Bram

that, while the majority of patients thought the inception of the disease had occurred within 3 or 4 years of their applying for treatment, nevertheless the actual duration of the condition had been much greater—these patients rarely seek medical attention until the syndrome has made inroads into the sense of well being and capacity to work. In these cases, Bram observed, the thyroid is generally enlarged though moderately, and in about one third of the series inspection revealed no swelling, deep palpation, however, disclosed in most cases an increase in size sufficient to warrant the application of the term goiter. Occasionally the symptoms were indicative of marked toxicity whereas the thyroid was not at all enlarged. Thus, as other workers have noted there may be no correlation between the size of the thyroid gland and the severity of the symptoms. The basic pathology in most of Bram's cases was hyperplasia, but adenomatous, fibrous, and even cystic changes were encountered rather frequently.

Hendrick (1941) observed that the majority of patients over 60 years of age who suffer from hyperthyroidism have adenomatous goiters, the findings of other workers have been in general agreement (see page 292). Plummer has found that adenomatous goiter is commonly present some 15 to 17 years before toxicity develops, indiscriminate use of iodine may be expected to hasten the process. In Hendrick's cases some of the adenomatous goiters were large. Patients who had received iodine during a lengthy period had thyroid glands whose hardness suggested a malignancy. Hendrick found that a definite goiter was present in every patient more than 60 years of age. Intrathoracic extensions were noted in a few instances, Bram reported a similar finding in his group of patients past age 50 but emphasized that any tendency for the gland to gravitate substernally is exceptional.

All observers have remarked the variety and frequent obscurity of the symptoms of hyperthyroidism in the elderly patient. The lower degree of stimulation in the elderly thyrotoxic patient may often stand in the way of early diagnosis. Thus, the basal metabolic rate may not be an indication of the true condition. The size of the gland may be but slightly greater than normal. The most frequent symptom seems to be weight loss, but obviously any one of a great number of disorders might be assumed to be involved rather than hyperthyroidism. The weight loss varies from a few pounds to about one half the weight of

the patient before the onset of the disease. The appetite may be excessive or it may be poor, depending upon the individual patient. Circulatory disorders are generally present along with the hyperthyroidism and, again, diagnosis may be difficult. Cardiac complaints, with palpitation and weakness on exertion, anginal symptoms and auricular fibrillation, as well as rapid heart action are frequently encountered in these cases. Most elderly patients have some degree of arteriosclerosis. Certainly these symptoms are not distinctive. Mental confusion or a psychosis may be attributed to senile changes in the brain. Tremor may be ascribed to some affection of the nervous system. The eye findings are by no means constant, only a small percentage of patients show exophthalmos and these cases almost invariably have a history of earlier development of exophthalmic goiter, this condition having eventually resulted in what Hertzler has termed "burned out" individuals. The apathetic or nonactivated case does not show stare, which may be present occasionally in the activated type of patient. Consequently, in many cases of hyperthyroidism in the elderly, the correct diagnosis may be forthcoming only after careful and perhaps somewhat prolonged study of the whole syndrome. To be sure, in many other cases, diagnosis of thyrotoxicosis in the aged may be simple, it must not be assumed from the foregoing that a considerable percentage of hyperthyroid patients in the upper age groups do not manifest all of the typical symptoms of the condition as encountered in younger individuals. Emphasis has been placed upon the atypical because of the frequency with which diagnosis has been missed in the past—largely because of the failure of the clinician to consider the possibility of masked hyperthyroidism in the aged, who present a great variety of complaints and disorders.

TREATMENT OF THYROTOXICOSIS IN THE ELDERLY

Patients in the upper age brackets have suffered great diminution in their reserves of vital capacity, their physiology has undergone regressive alterations and is now on a much lower plane than in youth; their biochemistry has been changed, and their reactions to drugs and to trauma (as of operation) are often far different from what they were earlier in life. These facts we must keep in the forefront of our minds when we contemplate the wisest therapeutic measures to be applied in cases of elderly patients with thyrotoxicosis. Degenerative

diseases may be so far advanced that surgery may be contraindicated, and only conservative measures may be applicable Crile (1938) reported that patients past 70 years of age and suffering from thyrotoxicosis may react well to thyroidectomy but postoperative complications are common, in one group of patients the mortality as a result of complications was as high as 21 per cent In selected cases, Crile recommended in this earlier report thyroidectomy may be performed in stages, under local anesthesia, otherwise, for the thyrotoxic patient past the age of 70, conservative measures are advisable In a later report (1940), Crile and Crile again emphasized the risks of operation in the elderly, in whom the basic processes of metabolism are frequently deranged and the mechanisms by which the disorder can be corrected have been damaged to such an extent that they cannot meet the demands resulting from surgery Hence a general metabolic breakdown with liver failure, uremia, delirium or a terminal pneumonia may follow operations performed with the usual techniques, preoperative, operative and postoperative Similar cautions have been expressed by most surgeons with experience in dealing with geriatric patients (Hendrick, 1941, Cattell, 1941) Eight patients out of Hendrick's series of 80 did not respond sufficiently to medical management to encourage surgical interference and all of the 8 died within a few months, these cases were distinguished by advanced cardiac damage Most of the other patients required meticulous preoperative care because of the coexistence of hyperthyroidism and one or more of the following conditions rheumatic heart, generalized arteriosclerosis, impaired renal function, prostatic hypertrophy with retention Such complications frequently indicated the advisability of stage operations, but with the best care, the operative mortality in Hendrick's group of patients past 60 years of age was 5.5 per cent (as contrasted with an operative mortality of 1.2 per cent in a large group of patients whose ages were below 60 years) Mora and Greene recorded 6 fatalities after thyroidectomy in their series of 200 cases aged more than 50 years, whereas in 860 cases below that age there had been but 1 death

There are several factors which must be stressed as of the utmost importance in relation to thyroidectomy in the elderly or geriatric patient Many thyrotoxic patients have become iodine fast, the administration of thiouracil may seem indicated in such cases to facilitate

preoperative management and preparation. Nevertheless, the risks involved in the administration of thiouracil to patients with adenomatous goiters may be serious unless thyroidectomy is to be total, as already pointed out in a previous section (page 158). The administration of iodine in iodine fast cases may be counted upon to provide the desired margin of safety at operation. Further, even in so called normal individuals past the age of 60 to 70 years, the common tests of liver function and kidney function often do not serve to indicate the degree of impairment of function. The possibility of liver failure or kidney failure must be carefully taken into account. It is well known that anesthetics in general have a toxic effect upon the liver, and in the aged the reserves of liver function have been lowered to what must be regarded as a dangerous extent. Two or 3 days after operation, confusion or delirium may ensue—as an indication of liver failure when the febrile reaction to thyroidectomy may be subsiding. Some evidence of jaundice is usually also seen in such cases, such as increased pallor, visible jaundice, and a rise in the icterus index. Preoperative diet (page 306) and postoperative diet (page 306) are therefore of outstanding importance in thyroidectomy. In cases of elderly patients, the reserves of the liver must be built up to the maximum extent possible.

Another great danger is that of a suddenly developing pneumonia; early symptoms must be watched for, and the administration of penicillin or the indicated sulfonamide should be considered immediately.

Whenever possible in operations upon the geriatric patient, the use of a local anesthetic is preferable to general anesthesia. Geriatrists generally have recognized the willingness and ability of the aged patient to undergo some additional inconvenience or distress to avoid the dangers involved in the employment of general anesthesia. Local anesthesia, of course, reduces the drain upon the reserves of the liver and as a rule does not weaken the other vital organs so much as does the use of a general anesthetic.

The elderly patient, moreover, reacts differently to sedatives than does the younger patient. Mental confusion frequently follows the administration of a barbiturate to the patient past 70 years of age. Such (slight or great) mental confusion may serve to obscure the onset of liver failure. Morphine is far more of a depressant in advanced years and should be used only in minimum dosage and with the greatest caution.

Finally, unless we are sure that the condition of the elderly patient is sufficiently ameliorated by preoperative care, we should hesitate to operate. The patient may show markedly exacerbated symptoms of hyperthyroidism despite optimum care, and we may at first think that operation is imperative as an emergency measure. Nevertheless, experience has demonstrated the wisdom of waiting. And in the meantime, roentgen therapy may serve to effect sufficient amelioration so that, in the course of a few weeks, surgical interference may be carried out, a maximum margin of safety having been attained.

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CHAPTER XI

PREOPERATIVE CONSIDERATIONS

WITHIN the past decade, preoperative treatment of the thyrotoxic patient has been improved immeasurably and the resultant striking reduction in operative and postoperative mortality has induced the establishment of an almost standardized system of preoperative measures whose value is now unquestionable. Of course, in the various clinics there will be found minor variations in preoperative treatment but there is universal recognition of the significance and indispensability of adequate rest, tactful control of psychic factors, optimal diet, adequate medication with iodine or thiouracil (or propylthiouracil) or both, adequate treatment of complicating disorders and wise timing of the operation with due regard to reduction in basal metabolic rate and to amelioration of other signs and symptoms of the toxicosis. It is almost universally realized that the cardiac patient and the elderly may in a large percentage of cases be placed under an excessive operative load when a bilateral thyroidectomy is performed, in such cases and in other cases which remain a poor risk despite optimal preoperative management, a two stage operation will usually be indicated. The surgeon who has dealt with large numbers of thyroid patients has learned how to avoid thyroid crisis in almost all cases, nevertheless, in the poor risk patient, the danger of thyroid storm remains ever present. Thyroid crisis may occur when least expected. The incidence of such severe reactions can be kept at a minimum only when all prophylactic measures have been meticulously applied. As results have proved the great safeguard against thyroid crisis is optimal management of the patient before operation — although to be sure, postoperative care as well as careful attention to the reactions of the patient during anesthesia and operation must also be regarded as of vital importance. The patient whose general condition has been brought as nearly to normal as possible and whose vital reserves have been increased to the maximum will withstand the strain of operation with the maximum margin of safety. In thyroid surgery, gratifying end results are attained when

the experienced judgment and skill of the endocrinologist, internist and cardiologist have assured the surgeon that operability has been brought to the highest possible level. Preoperative preparation of the patient is, of course, supervised by the surgeon, who makes the decision as to the optimal time for operation and upon whose knowledge and deftness the wellbeing of the patient depend in the ultimate analysis.

STUDY OF THE PATIENT

The study of the patient should include (1) careful eliciting of the history, (2) complete physical examination, (3) determination of the size, consistency, and mobility or fixation of the thyroid gland, (4) cardiac examination to detect possible signs of congestive heart failure, coronary occlusion, or angina pectoris, (5) laryngeal examination, (6) repeated basal metabolism readings, and (7) other laboratory determinations for evidence of diabetes mellitus, renal damage, and impaired hepatic function, in addition a blood count should be made. When the thyroid is more than moderately enlarged, a roentgenogram of the chest should be made, an intrathoracic goiter or adenoma may thus be revealed, as will any compression or deviation of the trachea. The eye signs and symptoms must be carefully noted. In some two thirds of hyperthyroid cases, some degree of exophthalmos is encountered, in this connection it should be remembered that many patients will have had naturally prominent eyes before the onset of exophthalmic goiter. The eyes should besides be examined for the common if not typical symptoms of puffiness of the eyelids, lid lag, poor convergence and other signs of eye muscle involvement.

Important information as to the toxic condition of the patient may be obtained in the majority of cases by observation of the extent of the nervous manifestations (restlessness, irritability, emotional instability). Tremor is as a rule fine and rapid, although in the occasional patient it may be as coarse and slow as in Parkinson's disease.

The more severely toxic patients may show gastro intestinal symptoms, such as diarrhea (less than 30 per cent of all cases) and nausea and vomiting. Persistent nausea and vomiting are very serious symptoms in the thyrotoxic patient and should be considered strong presumptive evidence of an impending crisis (Thompson, 1944).

The degree of muscle weakness and fatigability roughly corre

sponds to the intensity of the thyrotoxicosis. As the patient's condition improves during preoperative treatment, the patient's strength and endurance should increase, as one indication of improved operability.

As is well known, basal metabolism determinations are the outstandingly important means of ascertaining the degree of toxicosis and of estimating the improvement effected by preoperative management. Also, all experienced clinicians are well aware that a single basal metabolism test is not sufficient to show the patient's true condition before treatment is begun, a series of readings should be taken on successive days until the true metabolic level has been definitely determined. Whereas the basal metabolic rate often indicates the degree of thyrotoxicosis, in many cases it may not. Some patients, especially those with apathetic or masked hyperthyroidism may be severely toxic and yet have a normal or even subnormal metabolic rate. It may be stated as a general rule, however, that the higher the level of metabolism the more intense the toxicosis. A persistent elevation of the metabolic rate above 15 per cent is strong evidence that a thyrotoxic state exists.

Other Laboratory Tests The hippuric acid test frequently indicates the degree of impairment of hepatic function in relation to the degree of hyperthyroidism, in many cases the liver damage closely parallels the severity of the thyrotoxicosis. The galactose tolerance test similarly may be found helpful in determining not only the extent of hepatic dysfunction but also in supplying additional evidence that a hyperthyroid condition indeed exists. Blood iodine determinations, however, are of much greater significance (page 129), as previously mentioned they provide excellent evidence as to the extent of hepatic impairment and as to operability. Concerning blood cholesterol level it may be stated that, as a general rule — although one with many exceptions — the lowering of the blood cholesterol is in inverse ratio to the elevation of the basal metabolic rate, but, because of the numerous exceptions to this general rule, we cannot regard the blood cholesterol level as a reliable indication of the degree or even the presence of hyperthyroidism.

Importance of Experience and Judgment Clinical experience, judgment, and diagnostic ability are vastly more important than any laboratory test. Tests provide mere indications of the condition of

the patient and the effects of treatment. The physician or surgeon must study the whole clinical picture in order to reach an accurate conclusion concerning the patient's status, response to therapy, and optimal time for operation.

DIFFERENTIAL DIAGNOSIS

At times, it may be difficult to make a differential diagnosis between borderline or early hyperthyroidism or apathetic thyrotoxicosis and a number of other conditions, especially essential hypertension, lymphatic or myelogenous leukemia, acromegaly, and neurocirculatory asthenia. In pulmonary tuberculosis we may encounter the symptoms of loss of weight, marked fatigability and tachycardia, the basal metabolic rate being elevated when fever is present. In the absence of fever, however, the metabolic level is usually normal and the appetite is poor, a roentgenogram of the chest should demonstrate the lesion and laboratory tests should provide strong evidence that a state of hyperthyroidism does not exist.

In essential hypertension, the basal metabolic rate is in many cases elevated as much as 30 per cent. When a goiter is also present, differential diagnosis between hypertension and hyperthyroidism is exceedingly difficult. We may have to depend upon a therapeutic test with iodine, thiouracil or propylthiouracil and note the effect of the drug upon the basal metabolic rate.

In lymphatic and myelogenous leukemia the basal metabolic rate may be increased to as much as 70 per cent above normal. Tachycardia, increased sweating and even exophthalmos may still further confuse the clinical picture. Obviously a white cell count would provide almost decisive information, as would the characteristic signs and symptoms of the leukemias.

Acromegaly is a comparatively rare condition and in only a minor percentage of patients with this disorder do we observe a syndrome resembling that of exophthalmic goiter—goiter, high basal metabolic rate, tachycardia, palpitation, increased perspiration, tremor, exophthalmos. Indeed, in such cases, it is probable that excessive secretion of thyrotropic hormone by the anterior lobe of the pituitary has induced a thyrotoxic state (Thompson, 1944). When the skeletal changes featuring acromegaly have become obvious, the diagnosis is simple, but in the early phase of the disease it is practically impossible to determine

the true underlying condition. A therapeutic test with iodine or a thio drug would effect a reduction in the basal metabolism because of the presence of hyperthyroidism but would not disclose the coexistence of acromegaly. Thompson has remarked that accurate diagnosis is important because when thyrotoxicosis is associated with acromegaly, it is treated by attacking the pituitary and not the thyroid.

In neurocirculatory asthenia the less experienced clinician may be in doubt as to the correct diagnosis because of the symptoms of nervousness, tachycardia, increased pulse pressure, and marked fatigability. Generally, however, a goiter is not associated with this condition and the basal metabolic rate may be within the normal range. A therapeutic test with iodine or thio drug may be necessary to resolve the problem.

The differential diagnosis of diabetes mellitus and hyperthyroidism should rarely present much difficulty. The diabetic without hyperthyroidism has a good appetite yet loses weight, the patient, however, does not manifest the typical signs and symptoms of the hyperthyroid state. Of course, some patients have both diabetes and toxic goiter, in these cases we observe the characteristic manifestations of thyrotoxicosis and also find sugar in significant quantities in the urine. The double diagnosis may be confirmed by the sugar tolerance test. In a considerable percentage of cases, the nondiabetic hyperthyroid patient has traces of sugar in the urine or, occasionally, shows definite glycosuria (DeCourcy, 1928, see also page 320). In these instances, the sugar tolerance test rules out diabetes.

PRIOPERATIVE TREATMENT

The aim of the preoperative treatment of the thyrotoxic patient is to increase operability to the maximum possible by improving the patient's general physical condition, by reducing nervousness and apprehension by rest and informal psychotherapy, by optimal nutrition so that sufficient weight is gained, and by adequate medication with iodine or a thio drug (thiouracil, thiourea, or propylthiouracil) or both iodine and thio drug, to the end that the basal metabolic rate is brought down as near as possible to the normal level and other signs and symptoms of the thyrotoxic state are markedly ameliorated. Tachycardia should be diminished, the pulse pressure decreased and the abnormally high circulation rate significantly reduced. Muscular weakness, fatigability,

irritability, hyperkinesis, sweating, and tremor should be ameliorated. In the meantime, complicating disorders, especially cardiac conditions, diabetes, hepatic insufficiency, and infections, should be sought for and adequately controlled.

One should never be in a hurry to operate on a thyrotoxic patient. Only in very rare instances will thyroidectomy be an emergency operation. The ideal time for operation is indicated only by the response of the patient to preoperative treatment. The time is not just so many days or weeks after the institution of therapy with iodine with or without this drug. When the surgeon is sure that the maximum margin of safety at operation has been assured by the patient's improvement — and, of course, provided the amelioration of signs and symptoms is great enough, in accordance with definite criteria (page 315), the time for operation has come. Even then the improvement may not be satisfactory enough to justify a bilateral thyroidectomy, a 2 stage operation being necessary to ensure the safety of the patient (page 316).

Rest and Informal Psychotherapy As ever since the very beginning of modern treatment of hyperthyroidism the prime preoperative measure is rest of mind and body. In most thyrotoxic cases, the patient has been suffering for months or years with a sense of inability to react normally to the stresses and strains of everyday existence. The mind has been in a state of worry, hyperirritability, and distraction from emotional instability. The body has been in a state of tension, and strength and endurance have alarmingly decreased. The nerves and the heart have been deleteriously affected, as the patient is only too well aware, and so is usually cardiac conscious.

It is advisable (if not always possible) for the patient to be hospitalized for 2 or more weeks before thyroidectomy. If the case is one of apparently moderate hyperthyroidism, the patient may be allowed to sit up in a chair for a period each day and even to take short walks about the hospital or its grounds. In more severe toxicosis, the patient is put to bed and kept there, in absolute rest, for several weeks, this rule applies especially to patients in a state of cardiac decompensation or threatened crisis. It must be remembered that absolute bed rest may bring about severe muscle atrophy within a matter of days, at least some exercise, when it can safely be taken, is decidedly beneficial.

Physicians and nurses should be cheerful, and they should take

pains to utilize tactfully every opportunity to raise and maintain the patient's morale and to minimize the tendency to worry about domestic financial, or other troubles. They must gain the patient's confidence and allay apprehension in regard to the operation—the safety and advantages of which can be emphasized. We should keep in mind the fact that the hyperthyroid patient is a hypersensitive individual and has a capacity for suffering which is not possessed by those of a more phlegmatic disposition.

Diet The diet must provide approximately 5,000 calories per day in the average adult thyrotoxic patient. Men with severe hyperthyroidism require as much as 6,000 calories, daily. Many of the symptoms of thyrotoxicosis are at least in part the result of a prolonged negative caloric balance, intake of calories must exceed output, in order to build up the general health, overcome muscle weakness and increase endurance. A high carbohydrate diet supplies calories in quantity and ensures increased storage of liver glycogen (so that liver deaths are avoided). An excess of fat may cause diarrhea. Although protein has a relatively high specific dynamic action, the daily allowance must be at least one gram of protein per kilogram of body weight (estimated normal weight), the slight increase in heat production accompanying an increase in the protein content of the diet is probably a negligible factor as compared to the great advantage of ensuring an adequate supply of amino acids with which muscle tissue can be built up. In extreme cases, when it is necessary to increase operability in a patient upon whom an operation must be performed despite failure to respond satisfactorily to preoperative treatment, the employment of intravenous amino acid alimentation over a period of a few days may be of value (Lilman, 1940, Cole, 1944).

Thiamin requirements are proportional to the amount of food metabolized, and the administration of this vitamin has been shown to be of value in the nutrition of the thyrotoxic patient (Cowgill and Palmieri 1933, Means, Hertz and Lerman 1937, Williams et al 1943). The increased need for other B vitamins (pantothenic acid and pyridoxine) has been demonstrated by Drill and Overman (1942).

Calcium, phosphorus and vitamin D—probably best supplied by vitamin D milk—are believed to be necessary also in more than usual quantities (Puppel and others, 1945). All thyrotoxic patients have a tendency to lose calcium, with which element phosphorus metabolism

is closely associated, vitamin D, of course, promotes the normal utilization of calcium

Generally, fluid is provided in large quantities, up to 3 or 4 liters per day, but if edema appears as a result of a cardiac condition, the fluid intake should be decreased until the heart function improves. In rare instances, hypodermoclysis may have to be employed in the event that there is intolerance of orally administered fluid.

Vitamin K may be indicated in case of hepatic dysfunction or gall bladder disease. As is well known, adequate vitamin C (ascorbic acid) intake is essential for normal healing of wounds.

Treatment of Complicating Disorders (1) *Cardiac Conditions* Tachycardia with regular rhythm and without cardiac decompensation generally requires no other treatment than rest and medication with iodine or thiodrug or both depending upon the routine of the clinic; the same rule holds true for tachycardia with moderate decompensation, exceptions being made at times in the case of the elderly patient. Digitalis may be advisable in the elderly with regular rhythm and no signs of failure but with a cardiac capacity no greater than the load. Digitalization is also indicated, as is universally recognized in cases of obvious congestive heart failure or of auricular fibrillation with rapid pulse or persistent pulse deficit. Clute and his associates (1944) have stressed the importance of leisurely digitalization of patients who have had repeated attacks of transient auricular fibrillation; otherwise postoperative recurrence of the auricular fibrillation is almost certain.

(2) *Diabetes Mellitus* According to Regan and Wilder (1940) 17 per cent of patients with diffuse toxic goiter and 56 per cent of patients with toxic nodular goiter have diabetes as a complicating disease. Operation should not be undertaken until the degree of the diabetes and the insulin requirement have been carefully ascertained. Borderline diabetes is often ameliorated as a result of thyroidectomy.

(3) *Hepatic Insufficiency* Impairment of liver function is common in hyperthyroidism (page 136). Inadequate treatment may result in thyroid crisis and death. A high carbohydrate, high protein diet, and intravenous glucose are essential to the rebuilding of the hepatic reserve, to increased storage of glycogen, and improvement of hepatic function.

(4) *Infections* Untreated infections greatly increase the risk of thyroid crisis. When patients are brought to operation, they should be

free of active infection especially of the throat or respiratory system. If there is an active infection and sulfonamide therapy seems to be indicated, the condition of the hyperthyroid patient must be carefully taken into account, these drugs not infrequently have toxic effects on the liver, which may already be damaged in thyrotoxicosis. Nevertheless an acute infection may threaten to produce a thyroid crisis and the use of the appropriate sulfonamide may be life saving despite the possibility or the probability of increased injury to the liver. When sulfonamide therapy has been necessary, the operation should be postponed until the condition of the patient during a prolonged period of hospitalization has remained satisfactory. Fortunately, penicillin may now be employed in the treatment of many types of infections whereas formerly only the sulfonamides were available, for certain infections however, the sulfonamides are still the sole satisfactory remedy.

Iodinization A few years ago after the introduction of preoperative medication with thiouracil, thiourea and other thio drugs in Graves' disease, it was widely stated that the preoperative treatment with iodine had been outmoded. Nevertheless, as several times before in the history of the use of iodine in therapy of exophthalmic goiter such a conclusion has turned out to be erroneous — because based upon false assumptions as to the effects of iodine in this condition (page 142). The history of the utilization of iodine in goiter extends back through the centuries (see page 14). Not inconsiderable employment of iodine in Graves' disease was a fairly common procedure at the beginning of the century, but the pronouncement of the internationally famous Theodore Kocher in 1910 led to the almost universal abandonment of such medication, early misuse of iodine and over dosage, as well as a misunderstanding of the nature of the reaction to iodine therapy in thyrotoxicosis led to this warning of Kocher and similar pronouncements in the succeeding decade. The extended observations of Plummer (1923) again, and with irrefutable success demonstrated the value of iodine administration to goitrous patients. Still, even today, doubts are expressed as to the wisdom of iodine administration and as to the dangers involved in such (preoperative) therapy of thyrotoxicosis.

So once again, iodine therapy in toxic goiter has been dispensed with only to be restored to its former status as an indispensable aid to

treatment The value of iodine administration — even when thiourea, thiouracil or propylthiouracil is given as the so-called main preoperative medication — has once more gained almost universal recognition

It may be reaffirmed, as we pointed out more than a decade ago (DeCourcy, 1933) Of all therapeutic procedures for the cure of goiter, subtotal thyroidectomy has proved by far the most efficacious With improved technique we have succeeded in obtaining quicker convalescence and a lower mortality than formerly The mortality has been less than 1 per cent in all cases Of greater importance, however, has been the preoperative preparation of the patient with iodine This preparation, we have found — and our findings have received ample confirmation — overcomes the greatest obstacle to successful thyroidectomy, namely, the toxic phenomena and cardiac depression of exophthalmic goiter, which are so subject to aggravation by the emotional experience of the operation and the operative load

Our practice has been to administer 10 minims of Lugol's solution 3 times daily for 2 to 4 weeks prior to operation, the dosage and period of preoperative medication depending upon clinical improvement and changes in the metabolic rate reading

With this treatment, the patient improves progressively for 10 to 20 days Nervous tension is relieved and apprehension is replaced by serenity The symptoms of thyrotoxicosis gradually subside tachycardia is lessened, tremor is abated, weight is increased, and the basal metabolic rate falls toward normal In approximately 2 weeks (on the average), the patient who was formerly critically ill becomes comparatively well

As experience has shown, this improvement is only temporary If iodine medication is continued for any considerable length of time, or is stopped, no matter which, the patient suffers a relapse to his former condition

The point of the treatment, however, is that it enables us to improve a desperately sick patient to such an extent that he can withstand the shock of a serious operation Thus he becomes a much better surgical risk The patient at this stage may be operated upon with safety and, in most instances, with little or no untoward reaction On the other hand, if thyroidectomy is performed without previous

iodine (or thio drug) medication, the postoperative reaction is frequently severe, the temperature rising to 106° or 107° and in many cases has a fatal termination

In our experience, nothing else contributes so much to lowered mortality from thyroidectomy as preoperative treatment carefully carried out (DeCourcy, 1939) The aim is to operate at exactly the time when maximum improvement has been obtained This may require 10 days of medication, or in some cases 3 weeks or even longer

Patients operated upon while they are saturated with iodine do not suffer severe postoperative reaction We feel no apprehension in operating upon a subject who has been treated adequately with iodine

It has been our practice in operating on cases in which iodine has been given over a long period, but in which toxic symptoms are still manifest, to give $15\frac{1}{2}$ grains of sodium iodide intravenously immediately after operation—while the patient is still in the operating room Fifty minims of Lugol's solution are administered by rectum as soon as the patient returns to bed, and this procedure is repeated in 8 hours If the temperature rises above 102° on the following day Lugol's solution is given by mouth every 4 to 6 hours

It is very important, as a prophylactic measure, to continue treatment after operation, until all danger of a secondary reaction is past It is our practice to give 10 minims of Lugol's solution daily for 8 weeks after the postoperative reaction, following which medication the administration of desiccated thyroid is instituted as a prophylactic measure against recurrent hyperthyroidism (page 401)

Various opinions have been expressed as to the value of suspending iodine administration when uncontrollable conditions have necessitated the giving of such medication beyond the usual period, possibly for many weeks when the patient does not appear to be operable It would seem wise, under such circumstances to keep the patient in the hospital and wait for some remission, at which time operation may be performed with a sufficient margin of safety in most instances Exceptionally, in such severely toxic patients, a rest period of some weeks—suspension of iodine medication—may be indicated The employment of thiodrug medication may be especially advantageous in these cases

Most authorities agree that, after iodine therapy and before operation, the basal metabolic rate should be less than 50 per cent above

normal, but, as is universally realized, basal metabolic rate is by no means a sure indication of the degree of thyrotoxicity in a given patient. Its determination is of value when other factors — such as the clinical picture and the blood serum iodine — are taken into consideration at the same time. The significance of serum iodine is discussed at some length in another chapter (page 121). Patients with a basal metabolic rate of more than 50 per cent above normal must be considered as definitely poor operative risks, so high a metabolic rate may be assumed to be indicative of a severely toxic condition. In the average patient, as the symptoms show improvement under iodine medication, the basal metabolic rate falls 20 to 50 points provided, of course, that nutritional and other preoperative measures are adequate.

Most clinicians believe that cases of nodular goiter with toxicity respond more slowly to iodine therapy, not only is the response less marked but it is also less certain. Many authors have expressed the conviction that administration of iodine to patients with toxic nodular goiter may at times result in an exacerbation of symptoms. Cole (1944) has reported a consistently higher mortality rate following thyroidectomy for toxic nodular goiter than following operations for diffuse toxic goiter.

In a recent review of the dangers of the incorrect use of iodine in the treatment of goiter, Fitzgerald (1944) stated that there are 3 types of patients in whom he had observed the production of an apparent iodine thyrotoxicosis: (1) goiter in adolescence, (2) cases of exophthalmic goiter receiving iodine medication during a prolonged period, and (3) cases of nodular goiter. This writer concluded that iodine therapy should be reserved strictly for cases of diffuse goiter with toxicity. Nevertheless the consensus is that, as a rule, iodine medication may be advantageously used to reduce the toxicity of toxic nodular goiter to within operable limits.

Barker and Wood (1940) have made a study of the (relatively rare) adverse reactions to iodine, i.e., of iodism or sensitivity to iodine. Guptill (1942) listed the following reactions: (1) macular papular dermatitis which may progress to bulbous and ulcerative lesions if iodine administration is continued, (2) diffuse erythema and swelling when iodine comes into contact with presumably normal skin, (3) true allergic manifestations — fever, irritation of all free mucous membranes, dermatitis, and nervous irritability.

Some 3 per cent of patients with Graves disease do not respond favorably to iodine therapy (Means and Lerman, 1931) In practically all patients, continued use of iodine past a period of 4 or 5 weeks must be expected to cause an intensification of symptoms Discontinuance of iodine therapy, on the other hand, is followed by a worsening of the condition of the thyrotoxic patient (unless, of course thyroidectomy has been performed), the basal metabolic rate rises and the general symptoms approximate in their severity those existing before medication was begun It is true that many 'cures' have been reported to result from iodine therapy alone in exophthalmic goiter, but practically all authorities believe that if actual cures do eventuate they are decidedly exceptional In this connection it must be remembered that, in thyrotoxicosis as in a great many other diseases, spontaneous remissions do occur We have all seen cases, unoperated, which have subsided to leave only slight exophthalmos as evidence of the former condition

Iodine in Conjunction with Thio Drug Early investigations of the effects of goitrogenic drugs — especially thiourea and thiouracil — seemed to demonstrate that preliminary treatment of the thyrotoxic patient with iodine retards or prevents the action of the thio drug (Bartels, 1945, Eaton, 1945, Reveno, 1944, Williams and Clute, 1944) It was soon observed, however, that thio drugs increase the difficulties of operation by rendering the thyroid gland excessively friable and thus increasing the tendency to operative bleeding Routine use of iodine in conjunction with thiouracil or thiourea has therefore been adopted almost universally (Means, 1946) Furthermore, it has been established that the preliminary iodine medication of thyrotoxic patients does not delay the action of thiourea or thiouracil, provided iodine therapy is not discontinued (Rawson et al, 1945, Danowski Man and Winkler, 1946) Rawson and co workers found that whereas thiouracil causes the hyperplastic thyroid gland of Graves disease to become even more hyperplastic and prevents the utilization of iodine by the thyroid, in spite of the blocking of iodine collection following thiouracil administration the use of iodine brings about some degree of involution of the thyroid gland in the thyrotoxic patient Danowski and his associates reported that iodine and thiourea (and presumably also thiouracil and propylthiouracil) have additive or synergistic effects in the treatment of hyperthyroidism According to these

authorities, iodine and thiourea produce a more pronounced remission during the first 3 or 4 months than is produced by thiourea alone. When iodine medication was discontinued, hyperthyroidism recurred in some patients maintained in remission previously by the administration of this drug and iodine together. Further, according to Danowski and his collaborators, the recurrence of the hyperthyroidism with omission of iodine medication in patients on combined therapy is positive proof that the administration of iodine may permit a smaller dose of thiourea to be effective. In view of the potential toxicity of all drugs of this series, the practical advantage from such reduction in dosage is obvious. The mode of action of thiouracil and its congeners is similar to that of thiourea and it would appear that the conclusions of Danowski and co-workers can logically be extended to medication with any member of the group of thio drugs. As noted in another section (page 135), the work of Rawson and others (1945) has indicated that iodine and thiouracil have independent inhibitory actions in thyrotoxicosis which seem to be additive.

Danowski and his associates observed that the quickest and most pronounced remissions occurred in patients who received iodine along with thiourea. Also, as we would like to emphasize, the treatment of hyperthyroid patients with a goitrogenic drug may reduce the concentration of the serum precipitable iodine to the vanishing point. Hence prolonged thiodrug medication may be expected to induce a hypothyroid state in a considerable percentage of patients. The lowest possible dosage of thio drug would seem to be indicated whenever medication is continued through an extended period. Use of iodine in conjunction with the goitrogenic drug permits reduction of the dosage of the latter.

Hypothyroidism should be avoided in the prolonged medication of thyrotoxicosis; the general reaction of the patient is certainly not to be desired, and, of course, there is the possibility that the development of exophthalmos may be promoted as hypothyroidism develops. When hypothyroidism does occur following prolonged treatment of hyperthyroidism with a thio drug, it may be necessary to administer desiccated thyroid or reduce the dosage of the drug, either procedure, however, may bring about a recurrence of the thyrotoxic condition. It is wise to remember that, as medication with thiouracil or one of its congeners is continued, the serum iodine falls more rapidly than does the basal

metabolic rate — determinations of the latter may not provide sufficient warning of the insidious development of the hypothyroid state. Determinations of the serum iodine should be regularly made and it is necessary to watch for early clinical symptoms of the onset of hypothyroidism: sensations of chilliness, evidence of psychomotor retardation, and, at times, marked gain in weight.

Some clinicians who have adopted the procedure of administering iodine in conjunction with a thio drug have also made it a practice to discontinue both drugs on the day of operation. Whether or not the omission of iodine at this time is the optimal or even a safe procedure cannot be stated until more experience has been gained. Possible recurrence of the thyrotoxicosis is not the only consideration. There is also the problem of postoperative hypothyroidism, discontinuance of the thio drug would seem advisable, but, as regards discontinuance of iodine medication at operation, one can scarcely formulate an opinion on the basis of considerations which have been investigated to only a limited extent thus early in the history of thio drug therapy.

Thio Drug Therapy The routine, the untoward side effects, and the results of medication with the various thio drugs now available have been considered at length in the chapter on these new therapeutic agents (page 149).

Thyroid Crisis Thyroid crisis, or thyroid storm, represents a severe reaction of the thyrotoxic patient in which there is a marked exacerbation of the toxic signs and symptoms and in which the condition of the patient is profoundly and alarmingly, if not fatally affected. Such reactions are most frequently seen in poor risk patients especially those with cardiac or hepatic disorder, or with both. Meticulous attention to the measures which serve to build up the patient's vital reserves is the best prophylactic. Important factors in precipitating a thyroid crisis are acute or persistent subacute infection, severe emotional strain, operation which places too great a load on the circulatory and respiratory systems, and undersedation as well as oversedation (see page 390). * The treatment is symptomatic: efforts to reassure the patient, proper sedation (but not in excess), oxygen or oxygen and helium, iodine, and counteraction of the rapidly developing nutritional deficiency, particularly with intravenous glucose.

* The warning signs and symptoms have been discussed on page 390.

PREREQUISITES FOR THYROIDECTOMY

Operability is determined in different ways by different surgeons. Nevertheless, it is universally recognized that the patient's condition must meet certain definite, minimum requirements before even a unilateral lobectomy can be performed. As many studies have shown, one great cause of a high mortality rate associated with thyroidectomy is poor timing of the operation. The time for operation is indicated by special criteria of improvement rather than by duration of preoperative treatment. Severely toxic patients often show alternate periods of so called remission and of relapse. With iodization, in such cases several weeks may elapse before the desired state of operability can be achieved and the time for operation is during a period of remission. With thiouracilization desired improvement may not occur for months. When in doubt as to the advisability of operation the conservative surgeon will postpone the operation until an adequate margin of safety has been assured.

PREREQUISITES FOR BILATERAL THYROIDECTOMY

A 2 stage operation is generally advisable in elderly patients, those with cardiac complications, and other poor risk cases. Otherwise, usually a bilateral thyroidectomy can be performed when the improvement in the patient's condition has met the following requirements:

(1) **General Physical and Mental Condition** The surgeon can safely reach the decision as to the time to operate only if he carefully studies the entire clinical picture. Thus, the patient's general improvement, as shown by amelioration of the outstanding physical and mental symptoms, must be adequately taken into account. The patient should have gained in strength and fatigability should have been reduced. There should have been a diminution of nervousness, irritability, and emotional disturbance. A confused mental state may indicate the possibility of crisis, in some cases as a result of marked hepatic insufficiency. The experienced surgeon has developed a sensitive ability to detect unfavorable signs or symptoms as he studies the individual patient.

(2) **Gain in Weight** Unless there has been a significant gain in weight, the severely toxic patient should definitely not be submitted to operation. Weight gain is of the utmost importance in every thyro-

toxic patient. Failure to show gain in weight is proof that the treatment has thus far been inadequate. The desired weight gain depends upon the weight which the patient had lost before therapy was instituted. If the weight loss has been only about 10 pounds the gain of 3 or 4 pounds may be sufficient, other factors being satisfactorily checked. But when the weight loss has been great—20 to 40 pounds—then the gain during preoperative treatment should range between 10 to 15 pounds at least.

(3) **Basal Metabolic Rate.** Operability has not been increased to the desired level when the patient's basal metabolic rate remains as high as 40 to 50 per cent above normal after iodination or treatment with a thio drug. So high a metabolic rate is a sign that reaction to operation will in all possibility be unfavorable.

(4) **Resting Pulse Rate.** Most authorities agree that the resting pulse rate should not be above 110 and preferably not above 100. If minor emotional stress or slight physical activity induces a tachycardia of 130 or above this sharp rise in pulse rate usually signifies that the degree of toxicity is still excessive. The factor auricular fibrillation must, however, be taken into account in patients whose toxicosis is (apparently) of moderate degree.

(5) **Complicating Disorders.** The patient should not be submitted to thyroidectomy until every complicating disorder has been satisfactorily treated. A considerable interval should intervene between the clearing up of an active infection and the operation, this rule is not infrequently vital when sulfonamide therapy has been employed with resultant further impairment of hepatic function.

POOR RISK PATIENTS—UNILATERAL THYROIDECTOMY

The patient with serious cardiac condition and the elderly, whose toxicity is often masked (deceptively unproductive of typical warning symptoms) must always be regarded as poor risks. The margin of safety is also low when one or more of the following factors cannot be successfully counteracted: high or rising basal metabolic rate, continued weight loss or failure to gain weight, high pulse rate, psychotic manifestations, active infection, marked hepatic insufficiency, renal damage, marked hypertension, crisis status, and general failure to respond to medication with iodine or thio drug. If thyroidectomy is necessary despite the discouraging clinical picture, it should be per-

formed in two stages — but only after the surgeon is satisfied that all possible measures have been taken to increase operability

ROENTGENOTHERAPY

A small percentage of severely toxic patients do not respond to preoperative medication with iodine and thiouracil or propylthiouracil, or react adversely to such treatment, and in these cases some benefit may be derived from roentgenotherapy. Cole (1944) has stated categorically. There is no truth in the statements offered by some surgeons that x ray treatment adds tremendously to operative difficulties. Very few, if any, adhesions are produced by x ray therapy. Nevertheless the firmness of the gland may be increased and, according to a number of reports, at least in the occasional case some adhesions may be produced. Depending upon the operative technique employed, the increased firmness of the gland may or may not be an advantage, increased firmness, or decreased friability, may reduce the chance of hemorrhage. During the first few days after radiation of the gland the severely toxic patient may manifest a severe increase in symptoms as in the case cited by Cole. Four to 6 weeks are required for the attainment of the maximum effects of preoperative roentgenotherapy. It is to be stressed, however, that this mode of treatment is but rarely indicated because of the high percentage of favorable results obtained by proper use of iodine and thiouracil or propylthiouracil.

In a recent study, Thompson and Thompson (1944) determined the effects of irradiation of the pituitary gland as a means of avoiding surgery altogether. They remarked that, whereas the results of treatment of thyrotoxicosis with these drugs and iodine (or radioactive iodine) are very important, such therapy does not attack the underlying cause of the disease. Thompson and Thompson undertook the investigation on the hypothesis that, in some patients with toxic goiter, the anterior lobe of the pituitary stimulates the thyroid gland to overactivity. Irradiation of the anterior pituitary in 38 cases of toxic goiter gave the following results: in 7 patients, the basal metabolic rate dropped permanently to within normal range, in 16 patients, there was a marked but temporary reduction in basal metabolic rate (the reduction ranging between 15 and 52 points). Fifteen patients, however, showed no response whatsoever. Obviously, these results would not suggest general employment of irradiation of the anterior lobe

of the pituitary gland either as a preoperative measure or as a means of avoiding operation. It may be true, however, that further study may bring to light some practical clinical application of such therapy.

BLOOD PRESSURE IN DISTURBANCES OF THE THYROID GLAND

The effect of thyroid secretion on blood pressure has not been given the attention which it would seem to deserve. The established scientific facts are scanty and have given rise to a diversity of views. Early workers observed a fall in blood pressure after intravenous administration of a crude extract of the thyroid gland (Galta, 1923), further, in most instances, feeding thyroid gland was found to produce an increase in the fall of blood pressure from center to periphery, as in aortic regurgitation. Clinical facts, however, rather than the sparse results of experimentation provide us with most of our information along these lines.

In Exophthalmic Goiter. In exophthalmic goiter the cardiovascular manifestations may be likened to those occurring in aortic insufficiency although the former are less in degree. The throbbing arteries of the head and neck — which in some cases shake the entire body with each cardiac systole — the rapid collapsing pulse, the alternate flushing and blanching of the skin and the presence of capillary pulse readily suggest this analogy.

With regard to blood pressure, the analogy still holds. Plummer (1915), Taussig (1916) and others showed that the systolic pressure is usually somewhat increased, whereas the diastolic remains normal or is slightly below normal. The result is an increase in pulse pressure which normally amounts to 50 per cent of the diastolic, to an average of 90 per cent of the diastolic pressure.

Taussig found a distinct difference between the blood pressure in the brachial and femoral arteries in exophthalmic goiter, as in aortic regurgitation, that is the blood pressure was considerably higher in the femoral artery than in the brachial. The systolic pressure averaged 37.3 mm higher in the femoral artery, the diastolic, 7.6, and the pulse pressure, 29.7 mm.

An odd symptom observed in aortic insufficiency is a distinct pulsation of the retinal arteries in the fundus oculi. This sign is also present in cases of exophthalmic goiter, and in the two diseases the mechanism

of its production is the same. It is the result of an extremely low diastolic pressure in the peripheral arteries with a disproportionately high pulse pressure, so that the small arteries are caused to pulsate visibly with each cardiac systole.

Relation of Blood Pressure to Basal Metabolic Rate. We have repeatedly observed in cases of thyrotoxicosis that the systolic and pulse pressures tend to increase proportionately with the basal metabolic rate. After successful operation, depending upon the duration of the disease before operation and upon the period of time since operation the fall in systolic pressure has been found to parallel the reduction in basal metabolic rate. When hypertension has existed for a long time in association with thyrotoxicosis the change in the vascular coats is such that blood pressure tends to diminish only very slowly.

Similar findings were reported by Troell (1926), who found a higher systolic pressure and greater amplitude of pressure — the latter running parallel to the increased metabolism — in exophthalmic goiter patients than in controls of the same age. After thyroidectomy, the blood pressure in Troell's cases likewise returned to normal.

Handel (1924) found a similar relationship between blood pressure and basal metabolic rate in cases of essential hypertension. In nephritic hypertension, on the other hand the basal metabolic rate was almost normal.

Mannaberg (1924) likewise found the basal metabolic rate to be consistently increased in 20 patients with essential hypertension whose blood pressure ranged upward above 180 mm.

It would appear, therefore, that there is a definite relationship between the blood pressure and the basal metabolic rate not only in exophthalmic goiter but also in other conditions not related to the thyroid gland.

We believe that the increase in systolic pressure is proportionate to the duration of the disease and the degree of toxicity, the duration of the disease being the more significant factor. Whether or not hypertension is directly caused by thyrotoxicosis has not yet been determined, but its association with this disease is so common that Graves disease must always be considered as a possible cause of high blood pressure, after more common conditions have been excluded.

The blood pressure changes in exophthalmic goiter may perhaps be considered as an adjustment to meet the demands placed on the body

by the higher metabolic rate. A higher level of metabolism and tissue breakdown necessarily requires a greater supply of oxygen to the tissues. To meet this demand, the blood must flow more rapidly. Hence the pulse rate is accelerated and the *vix a tergo*, in the form of the heart beat, is increased, while the peripheral blood pressure is lowered thus reducing the resistance to the onflow of blood.

In our studies at the Clinic, it was found that, in some 5 000 examinations, the blood pressure had considerable variations in other wise healthy people. It was noted that under different environmental conditions blood pressure varied. The blood pressure varied as follows: systolic, about 20 to 30 mm, diastolic, about 10 mm, and the pulse pressures varied to the same extent as the systolic pressure.

The average normal pressures according to our determinations between the ages of 15 and 60 years showed progressive increase from 110 mm to 135 mm. Diastolic pressures varied from 70 mm to 90 mm. We considered a variation of 15 mm above and below normal to be within the normal range and took into consideration postural changes, effect of work whether mental or physical, fatigue and emotional stimulation. The pressures sitting showed practically no change from those of recumbency, pressures standing showed an increase in the mean blood pressure and a marked decrease in the pulse pressure.

Toxic adenoma associated with high systolic and high diastolic pressures we have come to regard as having an unfavorable prognosis, but if the systolic is high and the diastolic comparatively low, then the prognosis is generally more favorable. These cases seem to resemble nephritis in their hypertensive aspects.

Hypertension and Glycosuria. The glycosuria occurring in the course of many cases of Graves' disease appears to bear a definite relationship to hypertension and also to emotional disturbances. Feinblatt (1923) reported that in 2 000 routine blood chemical examinations 81 patients were found to have a blood sugar level above 0.15 per cent, only 42 per cent of these patients were diabetic. It is known that a number of circumstances affect the concentration of blood sugar under normal and pathological conditions. Furthermore, the renal threshold for sugar varies in different individuals, so that no definite generalization is possible. In our observations of normal individuals it was impossible to elevate the blood sugar level above 0.17 per cent even by the administration of large amounts of glucose.

As emotional perturbation may cause transient hyperglycemia and the renal threshold may vary in the same person at different times, it has been our policy at the clinic not to form conclusions on the basis of a single blood sugar determination. We have found blood sugar present most often in those cases of Graves' disease associated with hypertension or other marked vascular conditions. We have come to regard patients of this type as potentially diabetic.

Some patients with Graves' disease showed glycosuria from time to time, although the simultaneous blood sugar reading was normal. When the sugar tolerance test was performed, varying curves were obtained. Some were normal, others were typical of diabetes.

In cases of hypertension and hyperglycemia associated with exophthalmic goiter, the emotional element must always be considered, but we have come to regard hypertension as the most important factor in causing hyperglycemia. When true diabetes mellitus develops in such cases, it usually runs a mild course, unless gangrene or other vascular complications set in.

Blood Pressure in Myxedema As a general rule, the pulse rate and blood pressure tend to rise or fall with the basal metabolic rate. Hence it is not surprising that in myxedema, a disease characterized by a marked reduction in the metabolic level, both pulse rate and blood pressure drop markedly.

Willius and Haines (1925) reported a careful study of their findings with reference to the cardiovascular apparatus in 142 cases of high grade myxedema. The basal metabolic readings varied from 10 to 44 per cent below normal. The average pulse rate in this series was 63, systolic blood pressure, 110 mm, diastolic pressure, 74, and pulse pressure, 36 mm.

After elevation of the basal metabolic rate by thyroid treatment until it averaged 4 per cent above normal, the average pulse rate rose to 77. The systolic blood pressure was then 113 mm, diastolic pressure, 68 mm, pulse pressure, 45 mm. In other words, the normal cardiovascular ratio was restored with the return of a normal basal metabolic rate.

Although they found numerous electrocardiographic abnormalities which disappeared under thyroid medication and also the deviations in blood pressure to which reference has just been made, Willius and Haines saw no evidence to justify the hypothesis that a cardiac syn-

drome characterizes myxedema, nor could they identify any particular cardiovascular lesion as due to thyroid insufficiency

That arteriosclerosis is a frequent complication of myxedema has long been known. But Fishberg (1924) has pointed out that, in spite of this common association, hypertension is not the rule in myxedema. It has been reported as an occasional accompaniment of this disease and, in some instances, reduction in the hypertension was observed to follow the administration of thyroid.

In myxedema frequent blood pressure readings are important as a means of presaging and also averting circulatory failure. *As systolic and pulse pressure fall proportionately, cardiac failure may be regarded as imminent when the blood pressure is reduced to a marked degree.*

As an indication of threatened circulatory disaster, in exophthalmic goiter, irregularities of the cardiac rhythm are more important than changes in the blood pressure. While the heightened systolic blood pressure places an increased burden on the heart in this condition, the great fall of pressure in the peripheral arterial field acts as a compensatory mechanism, serving to reduce the resistance against which the heart must pump.

In our experience with disorders of the endocrine system, the thyroid is the only gland — excluding the rare condition of Addison's disease — disturbances of which produce marked changes in blood pressure.

THE PROBLEM OF GOITER HEART

Is there such a disease entity as goiter heart? This is a question which is often presented to the surgeon who does many thyroid operations. Frequently he is asked, or asks himself, Does thyrotoxicosis actually induce structural changes in a heart previously normal? Or does it merely put an added strain upon a heart already defective the cardiac condition then for the first time becoming evident?

The cardiac complications of goiter were among the first to be noted by the pioneers in the study of thyroid disease. Increase in the basal metabolic rate, which is the most striking manifestation of thyrotoxicosis, is the cause of the tachycardia — the most common heart disturbance noted in conjunction with enlargement of the thyroid gland. A rise in the metabolic rate demands a greater supply of oxygen. To obtain this additional supply more blood must be sent to the lung.

for oxygenation. Acceleration of the heart rate is the only way in which this demand can be met.

Hyperthyroidism is regularly accompanied by an elevation of pulse pressure, especially noticeable in the exophthalmic type of goiter. The usual explanation of these and other phenomena (heat flashes, sweating and abnormal heart sounds) which are the recognized symptoms of thyrotoxicosis is that elevation of the rate of metabolism reacts upon the cardiovascular system in such a way as to produce this acceleration of the heart beat and increased systolic blood pressure.

Pathologic study of the hearts of goiter patients who have come to autopsy have not shed much light upon our problem. Though marked pathologic changes have often been found, it usually has been impossible to prove that they were the direct consequence of the thyroid intoxication. Hypertrophy, especially of the left ventricle, has been noted and recorded, but congenital anomalies, valvular defects or other cardiac lesions were generally present as well, making it impossible to tell with accuracy whether the thyrotoxicosis had any share in bringing about the structural defects or whether they were merely congenital or acquired lesions, the association with thyroid disease being largely accidental.

An analysis of the heart sounds reveals that the systolic murmurs over the heart region, heard best at the apex and at the third left intercostal space, are 'blowing' in character and often show variations in their transmission. Though the systolic murmurs at the apex very probably indicate a relative mitral insufficiency, the fact that they can only faintly be heard when the subject is resting with muscles relaxed and are entirely stilled when the thyrotoxic condition has been relieved would suggest strongly that the murmurs bear a very intimate relation to the circulatory rate.

It has also been noted that, when an adenomatous goiter is present *without* thyrotoxicosis, the presence of essential hypertension is really a forewarning of the occurrence of hyperthyroidism. The coincidence of an enlarged thyroid, the characteristic symptoms of non-toxic goiter and hypertension can be understood only as making up a syndrome preliminary to the cardiac condition of which hypertension is a regular accompaniment.

The cardiac hypertrophy which may be termed the chief *secondary*

heart complication of thyroid disease is in no way pathognomonic of goiter. X ray examination will show a general rounding enlargement not characteristic of any one ailment. Often the electrocardiogram will be perfectly normal, but more frequently there will be evidence of pathologic conditions in the left ventricle, very exceptionally in the right ventricle. Cardiac weakness will cause dilation eventuating in permanent enlargement.

Clinical observation, as well as pathologic study, has shown that the auricular fibrillation and flutter which are relatively common findings in thyrotoxicosis are transient rather than persistent in character. *Transient fibrillation is often seen after thyroidectomy.* In what is known as postoperative thyroid shock, a tremendous acceleration of the ventricular rate will be associated with it. Such paroxysmal fibrillation probably depends upon some degree of myocardial injury. The persistent type of fibrillation, which can be relieved temporarily by medication but tends to recur when treatment is stopped, is undoubtedly the product of a definitely and permanently impaired myocardium. Transient fibrillation may be brought on by overexertion and is often observed by the patients themselves to be directly associated with some exacerbation of the toxicity of the goiter.

We have noted that among our patients auricular fibrillation is more frequent when the toxic goiter is of the diffuse nodular type rather than of the hyperplastic (exophthalmic) type. The only explanation we can offer for this finding is that in the nodular type the intoxication is gradual, the process in most instances slowly increasing in intensity over a period of years. Patients suffering from this type of goiter are not often seen by the surgeon until the disease has been in progress for a long time. The average interval (as computed from our records) between the date the patient first noted the enlargement and the date of the operation was 16 years.

The hyperplastic cases, on the other hand, are far more fulminating. Because of the severity of the symptoms and the disability resulting from them, the hyperplastic goiter patient comes early for help. Our records show an average period of 16 months between onset and entrance to the clinic for this type of hyperthyroidism.

It is because these hyperplastic cases develop a symptom-complex which alarms the patients and his friends relatively soon after the inception of the disease that the operative results are uniformly better,

notwithstanding the greater severity of the condition. A gradual enlargement of the neck with slowly developing thyrotoxic symptoms does not cause any special inconvenience to the average person. Social and economic considerations are likely to influence him against going to the doctor. As time passes he becomes accustomed to the condition and so it is not until irremediable damage has been done to the cardiovascular system that a full realization of the gravity of the affliction is forced upon him. Such a patient will often be well on in the fourth, or even in the fifth decade of life, so that the heart trouble when it occurs in women is not infrequently considered a premenopausal manifestation and its real significance totally ignored.

When such a patient finally does come to the surgeon, the latter will be powerless to give the relief he could easily have afforded 5, 10, or 15 years earlier. The hyperplastic goiter patient, on the other hand, by seeking the early relief of hyperthyroidism by adequate surgery, will usually escape serious cardiac damage. It has been the experience of our clinic that auricular fibrillation, if of recent origin, disappears entirely after thyroidectomy and very seldom recurs. But if the fibrillation is of long standing, though it may disappear after operation as soon as the patient undertakes any unusual effort there is likely to be a return of the preoperative symptoms.

Decompensation should not, however, be regarded as a contraindication to thyroidectomy. For years goiter surgeons have recognized this fact and realized that, no matter what type of thyroid disease is immediately responsible for the decompensation, it will be a benefit rather than a detriment to the heart condition to abolish the source of intoxication.

A number of our patients who had decompensation before thyroidectomy was done are now alive and in good condition, as long as 12 to 14 years after operation. For the reasons previously outlined, the type of thyroid disease will, however, have a decided effect on the patient's life expectation. If the thyrotoxicosis has been present for a long time, there probably will be such structural changes in the heart that it cannot carry on its functions for any great length of time. How many of these patients may have had structural defects in their hearts before the thyroid became overactive, we have no accurate means of gauging, but it is probable that their number is not inconsiderable.

On the other hand, there is a sufficiently large number of patients

having decompensation before thyroidectomy who are permanently relieved of heart symptoms after operation to argue strongly in favor of the theory that there is such an entity as 'goiter heart'. This does not mean precisely the same thing as that condition seen in the endemic goiter regions of Europe, concerning which so much was written in the early history of thyroid disease. That type of 'goiter heart' was formerly attributed to mechanical factors, such as compression of the cervical blood vessels and the trachea, or to chemical factors — a special toxin supposed to be elaborated by the thyroid gland or the suppositious poisons which were held responsible for the overactivity of the gland itself.

These theories were, of course, largely abandoned when an understanding of the processes of metabolism became generally diffused among the medical profession. As no metabolic studies are available for these earlier cases, we have no means of knowing how important a factor mild hyperthyroidism may have been in the production of the cardiac state which was then called 'goiter heart'. At any rate, we now know that the thyroid deficiency seen so frequently in 'goiter regions' can of itself, by virtue of its effect upon blood pressure as well as upon the kidneys and the intima of the arteries, seriously affect cardiac function.

We have all probably had the experience, when examining for the first time a patient who has suffered for a long period from a slow growing hyperthyroidism, of finding a normal basal metabolic rate but an abnormal heart rate. We have no means of ascertaining whether or not the metabolism was abnormal before the patient came under observation. Neither can we be sure, especially if the patient is a woman in middle life, that the hyperthyroidism which we now find is wholly responsible for such cardiac abnormalities as are in no way distinctively the result of thyrotoxicosis.

Myocardial disease is a relatively common finding at that age period quite irrespective of thyroid conditions, and result from the vascular changes which then take place and for which we can assign no more exact cause than age. Nevertheless, the evidence at present available strongly indicates that a persistent hyperthyroidism, even if the initial examination shows no thyrotoxicosis, is a potential, if not an actual, threat to the integrity of the heart.

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CHAPTER XII

ANESTHESIA IN THYROID SURGERY

SUCCESSFUL thyroidectomy requires the judgment of the experienced anesthetist. Numerous methods of anesthesia for operations on the thyroid gland have been advocated and several different procedures have been found to provide satisfactory working conditions for the surgeon as well as safety for the patient. Since 1920, approximately 15,000 goiter operations have been performed at the DeCourcy Clinic under various methods of anesthesia. After a thorough trial of local anesthesia in 500 cases, and of ether and a number of other methods we have given all these up in favor of nitrous oxide and oxygen, which we began to use in 1925. Among its many advantages are the rapidity with which it takes effect, the promptness of recovery, and the easy regulation of dosage. With this type of anesthesia it is possible to deepen or lighten at will the degree of narcosis. Postoperative vomiting is infrequent and postoperative hemorrhage very rarely occurs.

The chief disadvantage of local anesthesia, which is favored by many on account of its lack of toxicity, lies in the fact that these patients, being very nervous and excitable, often cannot tolerate an operation done while they are in a conscious state. In addition, local anesthesia has often been found inadequate during the stage at which the lateral lobes of the gland are elevated, and the surgeon on the whole has less freedom for rapid manipulation.

Because of the frequency with which a damaged myocardium is present in these operations, an efficient airway is a *sine qua non* for their execution. This is best secured by the free flow of oxygen obtainable under nitrous oxide combined with oxygen, which can be given in any proportion desired, with variations from moment to moment according to need.

Nitrous oxide has a low toxicity. With oxygen in straight mixture, it is non explosive. These are additional advantages which are universally recognized.

Thyrotoxic patients have a high oxygen requirement as a result of

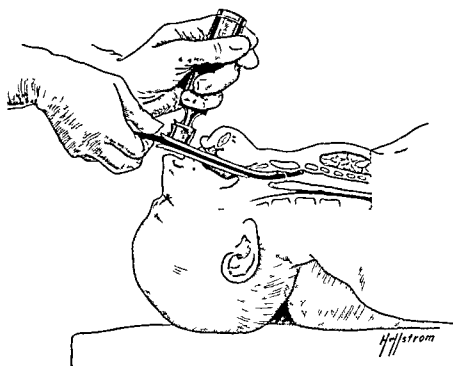


Fig 55 Intratracheal anesthesia Method of introduction of catheter

elevation of the basal metabolic rate, and anoxemia must be regarded as one of the greatest of all dangers in surgery of the thyroid gland. It must also be remembered that respiratory obstruction will increase the bleeding in the operative field. Even hyperextension of the neck, to obtain satisfactory exposure of the thyroid gland, tends to produce laryngeal obstruction. Any analgesic or anesthetic which promotes laryngeal spasm or otherwise may increase the probability of obstruction of the airway must be regarded as unsuited for operations on the thyroid. Postoperative reactions following the use of certain anesthetics must also be taken into consideration. And in these regards, it may be emphasized, nitrous oxide and oxygen anesthesia — as extensive experience has established — is eminently safe. The anesthetist skilled in the administration of this type of anesthetic has no difficulty in regulating precisely the depth of narcosis or in controlling any tendency to anoxemia.

INTRATRACHEAL ANESTHESIA

Intratracheal anesthesia should be employed in operations on intrathoracic goiters and may be indicated whenever there is marked deviation of, or pressure on the trachea. Obstruction of the airway is especially likely to occur during the extraction of intrathoracic extensions of the thyroid gland. Extraordinarily large goiters, large adenomas and extensive neoplastic growths may cause compression or deviation of the trachea sufficient to necessitate the employment of the endotracheal method of anesthesia. In secondary operations (as in recurrent hyperthyroidism), unilateral or bilateral paralysis of the vocal cords may be a factor, injury to the recurrent laryngeal nerves may lead to acute obstruction.

Because of the possibility of partial or complete obstruction of the airway during the course of the operation, it has been advocated by many surgeons that an intratracheal tray may be held in readiness whenever the thyroid gland is being operated upon. A laryngoscope and intratracheal tubes of different sizes would thus be quickly available in the event of emergency, and there would be but slight delay in establishing an airway. For thyroid operations on children, some regard intratracheal anesthesia as the method of choice.

A number of authorities have pointed out the danger that oxygen intake may become inadequate following heavy medication with opiates and barbiturates as basal anesthesia for a bilateral operation under local anesthesia. Intratracheal intubation and administration of oxygen (or oxygen and helium [Eversole], 1938) may become necessary.

Intratracheal anesthesia thus may serve to prevent dangerous respiratory embarrassment in patients with partially obstructed airways, the vicious cycle of hypoxia and narcosis, leading to serious anoxemia, may be avoided when obstruction occurs suddenly during the operation. When administration of oxygen has brought relief and the patient's struggle to breathe has subsided, usually the operation can be resumed safely under intratracheal anesthesia.

Roentgenograms of the neck and chest and examination of the vocal cords (if there is reason to suspect abnormal laryngeal function) should, of course, provide the surgeon and the anesthetist with the

information necessary to determine preoperatively whether or not there is any indication for intratracheal anesthesia

PRELIMINARY SEDATION

The nervousness, anxiety, and other psychic symptoms presented by the great majority of thyroid patients necessitate adequate preliminary sedation well in advance of operation. Such sedation serves not only to calm the patient, allay fears and bring the general emotional tone down toward the normal level, but also to lower the metabolic rate and heart rate. In all probability there also results some beneficial inhibitory effect upon the activity of the medullary portions of the adrenal glands. Many surgeons and anesthetists have consistently obtained satisfactory results with morphine sulfate and a barbiturate, such as pentobarbital sodium. Scopolamine hydrobromide may be administered along with the morphine. The depressant effect of morphine on the respiratory system is to some extent counteracted by scopolamine, which also depresses salivation, promotes amnesia and increases the narcosis induced by the former. Atropine may be used instead of scopolamine. The dosage of narcotics and sedatives must be varied, in all such preliminary medication, according to the age and condition of the patient (metabolic rate, vigor, degree of nervousness). Some clinicians prefer to administer basal sedatives by rectum, but desirable flexibility of administration may be afforded by the giving of divided doses hypodermically and orally. A common procedure is to administer pentobarbital sodium the night before operation in a dose of $1\frac{1}{2}$ or 3 grains (0.1 or 0.2 Gm.), so as to insure a good rest. The sedative may be administered again in suitable dosage on the morning of the operation, or it may be given a quarter hour after the hypodermic administration of morphine sulfate, $\frac{1}{4}$ grain (0.01 Gm.) and scopolamine hydrobromide, $\frac{1}{150}$ grain (0.0001 Gm.) when these narcotics are given an hour and a quarter before the operation. Pentobarbital sodium increases the sedative and amnesic effects of morphine and scopolamine. (Some authorities recommend that atropine, $\frac{1}{150}$ grain (0.0001), be employed rather than scopolamine.) For deeper narcosis when the patient reaches the operating room, it may be necessary to administer another dose of morphine and scopolamine (or atropine), or additional doses of pentobarbital sodium, in 2.5 per cent solution, may be given intravenously, depending upon the condition of the

patient Dosage and timing of administration of preliminary medication should be carefully considered so that the patient reaches the operating room in the desired state of drowsiness or somnolence

Intravenous pentothal has been found quite satisfactory by some surgeons and anesthetists for preliminary medication At the University Hospitals in Minneapolis, the following procedure has been favored For 2 or 3 days before operation, 1,000 cc of 5 per cent glucose in saline solution is given intravenously On the day of operation, the patient receives a liquid breakfast and intravenous glucose solution, just before the infusion is completed, intravenous pentothal is administered through the same infusion needle After the patient has fallen asleep, he is taken to the operating room, and inhalation anesthesia is begun (Rea, 1944)

ANESTHESIA IN OPERATIONS FOLLOWING TREATMENT WITH THIOURACIL

Frequently the thyrotoxic patient who has been treated with thiouracil for 2 months or more will be found to be in a state of hypothyroidism when he comes to operation It is necessary for the anesthetist to hold this possibility in mind In such cases the basal metabolic rate may have dropped below normal and there may have been a large gain in weight If hypothyroidism actually exists, it would seem advisable to administer only light premedication, no basal narcosis, and light anesthesia for the operation Postoperative sedation should also be minimal Heavy medication and deep anesthesia may be expected to cause undue depression when the patient is almost if not quite myxedematous rather than thyrotoxic On the other hand, it would appear unsafe to assume that, as a rule, all previously thyrotoxic patients are no longer in the hyperthyroid state when they come to operation after prolonged treatment with a goitrogenic drug

LOCAL ANESTHESIA

Local and regional anesthesia may be used successfully in a considerable percentage of thyroid operations Supplementation with a general anesthetic is generally necessary, however, and nitrous oxide and oxygen are to be preferred to other agents (Adams and Dixon, 1944) Adequate premedication is essential to control the emotional reactions of the patient, deep narcosis may be required, so the assump

tion that local anesthesia produces a minimum of secondary toxic effects would not seem justified in a large percentage of cases. In certain clinics, local infiltration of the neck is done in all procedures of thyroidectomy. Dinsmore and Shively (1941) have recommended the use of 0.75 per cent novocaine. Adams and Dixon have adopted the *method of blocking the superficial cervical plexus bilaterally with 1 per cent solution of procaine hydrochloride (or metycaine)*, the region of the incision being infiltrated with a 0.5 per cent solution of the same drug. When the lobes are being delivered and when traction is made on the thyroid gland, the discomfort of the patient must be relieved by administration of nitrous oxide and oxygen. In the aged patient, nitrous oxide and oxygen have been found most satisfactory in conjunction with local anesthesia, according to the experience of Dinsmore and Shively.

In patients who must be regarded as extremely poor risks, complete cervical block has been employed by some surgeons. One per cent solution of procaine or metycaine is injected bilaterally into the second, third and fourth cervical nerves and into the superficial cervical plexus and the region of operation is infiltrated with a 0.5 per cent solution of the same agent.

A vital problem in local anesthesia is that of the duration of the anesthesia. Because many thyroid patients are hypersensitive to epinephrine (and other vasoconstrictors), the use of a vasoconstrictor in the local anesthetic solution must be regarded theoretically as absolutely contraindicated. If, however, the patient is well prepared we have found that a small amount of adrenalin solution 1:1000 added to the anesthetic is not harmful.

ETHER

According to Adams and Dixon (1944), most surgeons agree that as a rule ether is not a desirable agent for routine use in thyroid surgery. They pointed out, however, 'if it is felt that an inhalation anesthetic agent is indicated (perhaps with an intratracheal tube) moderate amounts of ether may be administered with comparative safety to a patient for whom a gaseous anesthetic agent is inadequate. Cope and Welch (1912) also favored limited use of ether in these operations, and Nicholson stated more recently (1915). The test of time finds anesthetists returning more and more to ether anesthesia for thyroid

operations. The latter author expressed the belief that ether oxygen mixtures are especially valuable in anesthesia of thyrotoxic patients with signs of myocardial damage because of the comparative freedom from cardiac irritation when such mixtures are used. Certain surgeons and anesthetists have adopted the procedure of induction with a gaseous agent, maintenance anesthesia afterwards being provided by light concentrations of ether or a combination of ethylene ether or cyclopropane ether. The hazards of explosion have been emphasized by Horton (1941), who also has described in detail the precautions which must be taken.

ETHYLENE AND ETHER

Ethylene has been employed extensively at the Lahey Clinic (Nicholson, 1945), a mixture of 80 per cent ethylene and 20 per cent oxygen being used for rapid induction for ether anesthesia. Because of the inflammability and explosibility of ethylene, the same precautions as with ether become indispensable.

CYCLOPROPANE

Because anesthesia with cyclopropane can be maintained with a comparatively high concentration of oxygen and because postoperative recovery is rapid, this agent has received extensive trial in thyroid operations. Practically any abnormality of the cardiovascular system however, is a contraindication to the use of cyclopropane. Cope and Welch (1942) stated that this anesthetic is absolutely contraindicated in thyrotoxicosis, because of the frequency with which it induces ventricular fibrillation. Cole (1944) has expressed a similar conclusion. *Pharmacological studies have shown that cyclopropane has an apparent stimulating effect on the parasympathetic system, so that there may eventuate respiratory depression, extrasystoles in thyrotoxicosis, bradycardia, and, occasionally, ventricular standstill.* Such adverse effects may not be associated with the use of low concentrations (10 per cent) of cyclopropane in combination with oxygen (30 per cent) and ethylene (60 per cent), such mixtures have been employed with apparent safety in many operations in various clinics, for induction. Whereas cyclopropane is highly explosible, it has been stated that a mixture of the three gases in precisely these proportions is non

explosible Nevertheless, it would seem wise to remember that the proportions would change as the gases mix with air

INTRAVENOUS ANESTHESIA

During the past decade, intravenous pentothal sodium anesthesia has been employed more and more extensively for almost all types of surgery, and it has found favor among a considerable percentage of thyroid surgeons Under certain conditions, its use may have certain advantages not afforded by some other methods of anesthesia there need be no restriction to the amount of oxygen administered and, at least in certain cases, the metabolic processes of the thyrotoxic patient are not adversely affected Comparative freedom from nausea and vomiting has also been regarded as an especial advantage of pentothal sodium anesthesia But nitrous oxide and oxygen offer the same advantages without having the decided drawbacks of pentothal sodium used as the sole anesthetic agent Large amounts of pentothal sodium are required by hyperactive patients, so that postoperative sleep is unduly prolonged, with restlessness and excitation during recovery In intravenous anesthesia the laryngeal reflexes are usually still active Hence, where there is need to establish an airway quickly, as for obstruction of the respiratory tract, the insertion of an intratracheal tube may be difficult or even impossible without trauma In fact, laryngeal spasm may occur following anesthesia with pentothal sodium and cause obstruction of the respiratory tract Moreover, the drug characteristically causes some degree of respiratory depression

Intravenous pentothal sodium has been used to best advantage as an adjunct to other methods of treatment The drug has been employed to effect a rapid induction to inhalation anesthesia Satisfactory results have been reported in cases in which a combination of intravenous pentothal sodium and a mixture of 50 per cent nitrous oxide and 50 per cent oxygen was used A combination of 60 per cent ethylene and pentothal has been employed to some extent also Some surgeons have recommended the administration of pentothal sodium to unusually apprehensive patients, a local or general anesthetic being administered before operation According to Nicholson (1915), In the future, pentothal alone or in combination with one of the gaseous agents may enjoy a wide field of usefulness in the production of thyroid anesthesia *

TRIBROMETHANOL IN AMYLENE HYDRATE (AVERTIN)

Avertin has been used in a number of clinics as a non volatile agent for the production of basal anesthesia for thyroid operations, but it is generally recognized that there are many absolute contraindications to this drug in thyroid surgery circulatory disorders, renal conditions hepatic insufficiency (almost characteristic of the thyrotoxic state), and age (above 50 years) Some, however, regard avertin as of value in overcoming the purely nervous symptoms of certain thyroid patients, particularly certain psychotic thyrotoxic patients Others have stated that the drug is helpful in the form of heavy premedication of children with hyperthyroidism Nevertheless, it remains indisputable that response to avertin is unpredictable, counteraction of untoward effects is all but impossible once the drug has been administered, and, when used as a basal anesthetic, it generally fails to reduce the pulse rate of the thyrotoxic patient Cope and Welch (1942) listed the drug among the agents absolutely contraindicated in thyrotoxicosis and advanced the following explanation Avertin produces inadequate oxygenation through direct effect on the circulatory system and the respiratory center It also causes liver damage, an effect particularly undesirable in patients with impending hepatic insufficiency of thyrotoxicosis The toxic effects of avertin are similar to those of chloroform and ethyl chloride and include, besides those mentioned, damage to the renal tubules and possibly ventricular fibrillation

SPINAL ANESTHESIA

Spinal anesthesia has been employed not only in the management of postoperative thyroid crisis (Crile, 1936, Bartels, Stuart and Johnson, 1940) but also as an adjunct to the operative management of severe hyperthyroidism (Rea, 1944, Knight, 1945) This type of anesthesia was first suggested by the theory that hyperactivity of the adrenal glands plays a prominent role in the syndrome of hyperthyroidism In consonance with this theory, an effective spinal anesthesia should inhibit medullary adrenal releases during the operation and should therefore aid in preventing severe postoperative reactions Using a combination of intravenous pentothal and inhalation anesthesia (ethylene or cyclopropane) together with procaine (spinal anesthetic), Rea and also Knight found it possible to do bilateral sub

CHAPTER XIII

OPERATIVE CONSIDERATIONS

IN RECENT YEARS, the mortality rate associated with operations for thyrotoxicosis has been reduced to a very low level in the larger clinics, and this reduction is attributable in great part to improved preoperative medication with iodine and thiouracil or propylthiouracil adequate treatment of complicating disorders, proper timing of the operation, and improved postoperative management. Emphasis upon such factors, however, has tended to obscure the vital importance of the factors of surgical experience, knowledge and skill. The major operative techniques employed today have been worked out with exceeding care and brought nearer perfection during a period of decades. Obviously, no matter how good the preoperative and postoperative care the wisdom and skill of the surgeon remain the most important factors in the attainment of a very low mortality rate in thyroidectomy. The mortality rate in thyroidectomy will not be gratifyingly low in operations performed outside the special thyroid clinics until a greater number of general surgeons carefully study the details of and practice a standardized, up-to-date and safe technique whose value has been established by its results in a large number of cases.

Although at present there is a trend toward the exclusively medical management of toxic diffuse goiter with thiouracil or propylthiouracil surgery nevertheless remains the established, sure approach to the highest rate of permanent remissions or cures. In view of the prolonged period of medication with a thio drug and in view of the percentage of relapses (early or late) as recorded in the newer literature thyroidectomy would seem to be still not only the surest but also the most convenient and least expensive safe method of treating toxic diffuse goiter.

As regards toxic nodular goiter, there is no doubt that thiouracil or propylthiouracil bring about a gratifying amelioration of symptoms and signs of toxicity. But no drug that will remove a nodule or adenoma

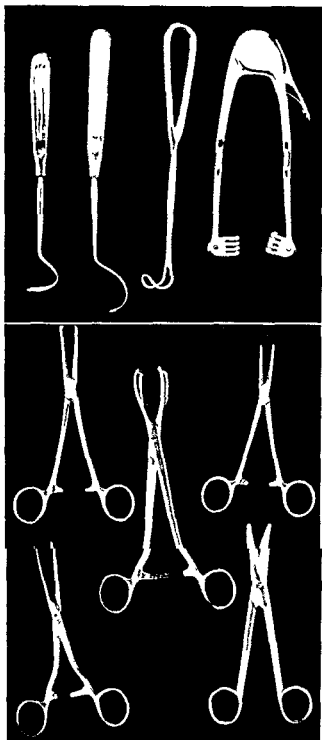


Fig 56 Special instruments used for thyroidectomy

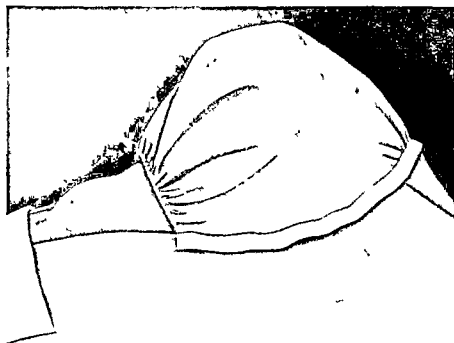


Fig. 37

Fig 37 Sterile mask

from the thyroid gland has as yet been discovered. The danger of the development of carcinoma is ever present — and, indeed, may even be increased by medication with a goitrogenic drug (page 158) unless a thyroidectomy is performed.

Further, and we feel that this point must be stressed, against the possibility that at least a certain percentage of physicians inexperienced in the treatment of thyroid disease may be tempted to treat every goiter or thyroid tumor with one thio drug or another. Surgery — early surgery — is definitely indicated in cases of discrete adenoma, intrathoracic goiter, thyroglossal tumors, cysts and sinuses, lateral aberrant thyroid bodies, and, of course, all types of cancer of the thyroid gland.

Our experience in thousands of cases has enabled us to develop, refine and standardize the operative techniques described in the following pages. Our work has, of course, benefited greatly by the improvements suggested by the reports of leading surgeons, although naturally our own findings and operative results have led us to design

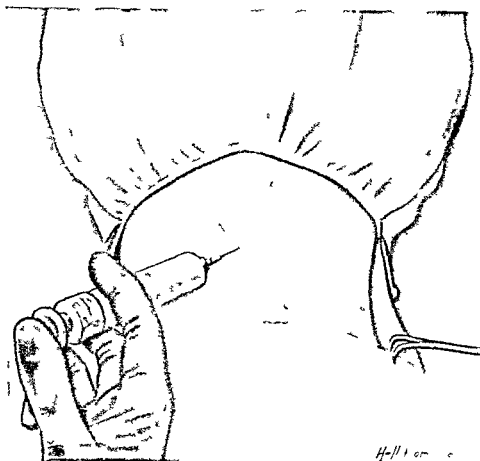


Fig 58 Local anesthetic

and progressively to develop our own special modifications of fundamental procedures and to work out original basic refinements whose value has been established by operative results and follow up studies through extended periods of time

TECHNIQUE OF BILATERAL THYROIDECTOMY

1 With the patient in the reverse Trendelenberg position, the incision is usually made in one of the lower creases of the neck. It should however not be so low as to sag down at a later time below the natural lowest skin crease. Too much curvature is to be avoided. The knife should be drawn across the neck with an arm motion, which does not bend the hand at the wrist so as to prevent a feathering of the skin margins and thus to permit a better connective result. The incision

should be carried through the closely adherent platysma to facilitate blunt dissection (Fig 59)

Small bleeders or oozing spots in the skin flap are grasped with small hemostats and coagulated. This procedure eliminates ligation which frequently becomes troublesome later because of cystic accumulation about the catgut.

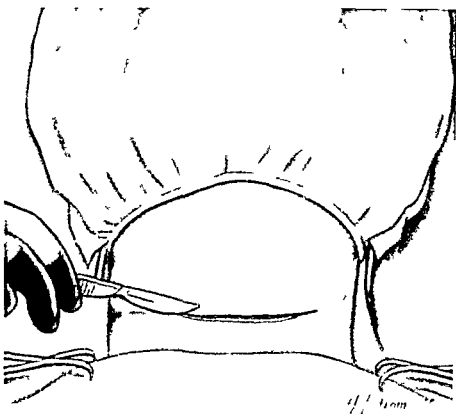


Fig 59 Incision through skin and platysma

Care should be taken to cut into the fascial plane between the platysma and fascia on the anterior surface of the ribbon muscles. In order to avoid severing the cutaneous nerves, which accident would result in later numbness and in paresthesias that sometimes extend from the chin downward, the skin flap should not be raised laterally more than just enough to make a V between the lateral ends of the incision and the highest point of the midline.

2 It is seldom necessary or desirable to sever the ribbon muscles,

but in the hands of a less experienced operator such a division may for a time be the safer course until greater proficiency is gained. In such a case, the division should be made high up and as near the larynx as possible in order to reduce the possible damage to the nerve supply of the upper portion of the muscle. After experience has been gained sufficient visualization is obtainable if the longitudinal incision of the fascia is carried well up over the laryngeal cartilage (Fig 60). Previous to the days of iodization it was difficult to raise the hyperplastic gland and therefore necessary to divide the ribbon muscles.

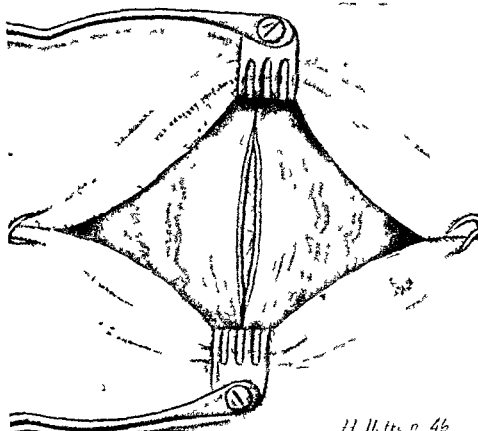


Fig 60 Longitudinal incision of fascia

Occasionally today we divide the muscles when operating on very large substernal goiters or those which because they are iodine fast fail to undergo colloid involution. These indications are however relatively rare.

3 Blunt dissection over the gland with the fingers facilitates delivery. No attempt is made to go around the gland, because in doing this there is danger of tearing the lateral vein and also of traumatizing the recurrent laryngeal nerve (Fig. 61)

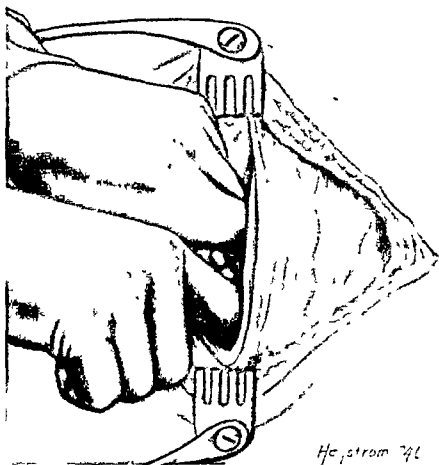


Fig. 61 Freeing of gland from overlying structures

A definite strip must be left on each side toward the back of the gland, in order to preserve intact the parathyroids and the recurrent laryngeal nerve. If by chance a parathyroid is damaged, the accidentally dissected gland should be immediately reimplanted. One should avoid the removal of any fat like processes, because the exact position of the parathyroids is not always predictable. In the event of injury to the laryngeal nerve, as revealed by a change in the type of breathing

the nerve should be repaired at once, if it is cut, it must be sutured. If a clamp is exerting pressure on it, the clamp must be removed.

4 Elevation of the right lobe can usually be accomplished to a point sufficient to apply the traction forceps by use of a mouse tooth tissue forceps. After applying this and elevating the lobe with the

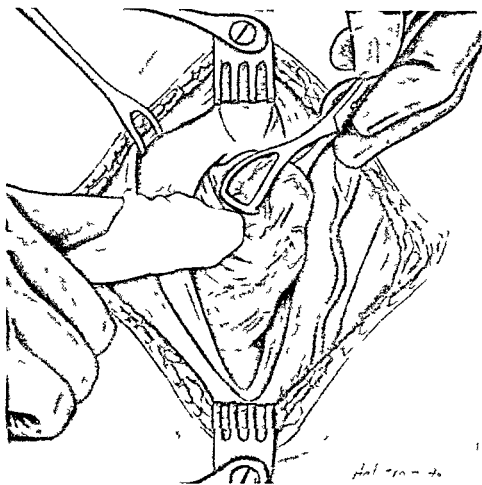


Fig 67 Wiping down capsule

traction forceps the sternothyroid muscle, which is adherent to the side of the gland is wiped down with a piece of gauze as the lobe is being elevated.

5 The superior pole is next dissected free and a double strand of No. 2 chromic catgut passed above the pole and tied, thus the superior artery is secured. Before the carrier is passed around the pole, the

latter is elevated by passing the finger underneath and raising it (Fig 63)

Because of the close proximity of the superior laryngeal nerve some surgeons feel that it is necessary to dissect out the superior artery and tie it under direct vision

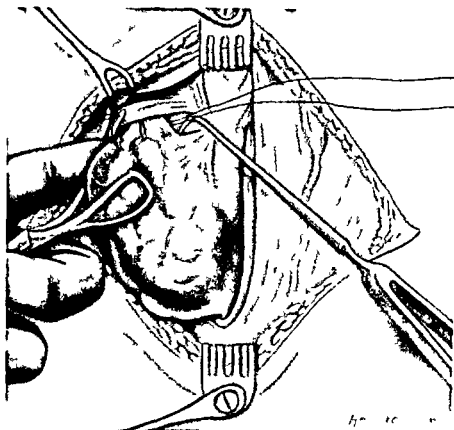


Fig 63 Ligation of superior pole

In doing a number of dissections on the cadaver we have found this to be unnecessary and undesirable for 2 reasons. First the artery frequently divides some distance above its entrance into the gland and there is some danger of injuring the nerve because of the added trauma. Second because of the poor exposure at this point retraction of the artery frequently occurs after the clamp is applied and makes ligation not only difficult but also hazardous besides slipping of the knot is encouraged so that primary or secondary hemorrhage may result.

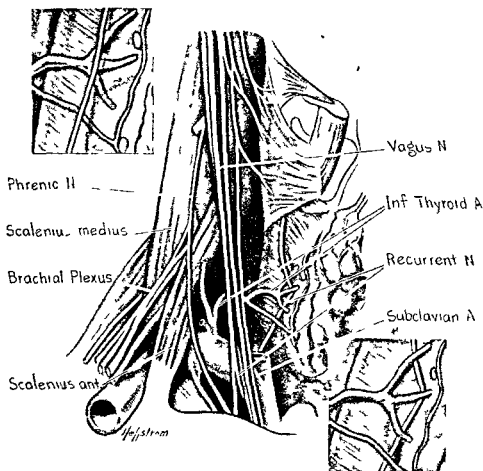


Fig 64 This illustration shows the various relationships of the recurrent nerve to the inferior thyroid vessels. Also the trianguloid depression where the inferior thyroid artery enters the gland. This depression if carefully avoided in placing the clamps along the lateral surface of the lobe will absolutely prevent injury to the recurrent nerve or the parathyroid glands.

If the finger is passed under the superior pole and the pole is raised, the carrier is passed only around the vessels and there is no danger to the nerves or trachea. In the examination of 10 cadavers ligated in this manner with subsequent inspection, the superior laryngeal nerve was not included in the ligation in any instance.

6 After the elevation of the right lobe and ligation of the superior artery, the superior pole is incised with a knife proximal to the ligation. This incision facilitates further elevation of the gland and permits more even dissection, thereby lessening the chance of leaving too much

glandular tissue at the superior pole and favoring a recurrence at this site

Straight mouse toothed hemostats are applied along the side of the gland at right angles to the trachea. These hemostats clamp the branches of the inferior artery and veins as they penetrate the gland.

We have devised and extensively employed a modification of the usual procedure in the placing of these clamps (Fig. 65). To make

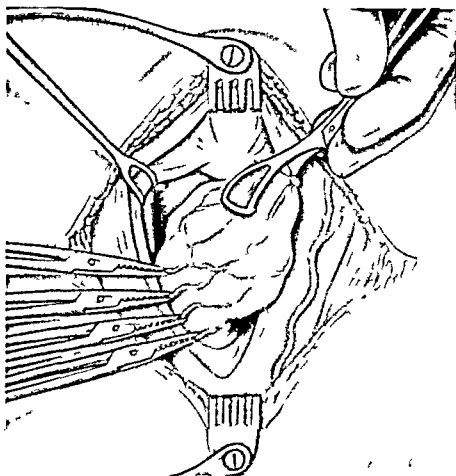


Fig. 65 Hemostats on branches of inferior artery and vein

doubly sure that the clamps in every instance bite into thyroid tissue as we reach the triangular depression at the site where the inferior thyroid artery branches to enter the gland we place the clamps around and slightly but definitely beyond the rim of this depression. This

refinement in technique greatly aids in reducing to a minimum the risk of damage to the recurrent nerve

The trunk of the inferior artery is not exposed. We still feel that the ligation of this trunk lessens or entirely destroys the blood supply of the parathyroid bodies and encourages the development of tetany.

The question of the amount of gland to remove is always controversial. It is better to remove too much than too little because the remaining portion will usually hypertrophy to an extent sufficient to maintain normal body metabolism. As a rule in our opinion, not less

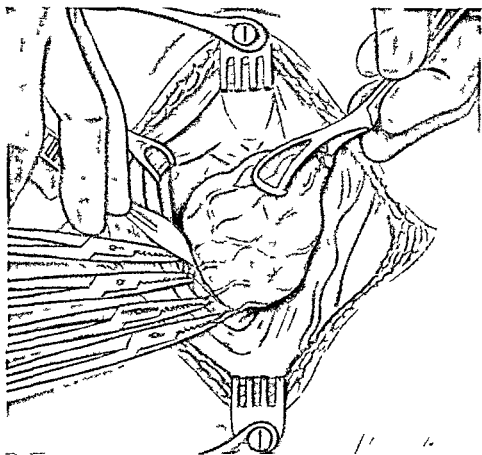


Fig 66 Incision of right lobe

than four fifths of the gland should be removed if thyrotoxicosis is to be relieved, but of course, the amount varies with the individual case. A practical way is to place the hemostats so that they will lie on a

plane with the anterior surface of the trachea when the gland is elevated at the time the clamps are placed

7 The right lobe is then dissected from without inward until the trachea is reached. The surgeon then usually disregards the right lobe and proceeds to dissect the left lobe leaving the trachea until the last. Instead however, we continue the dissection of the right lobe all the way across the trachea and slightly under the left lobe. When the

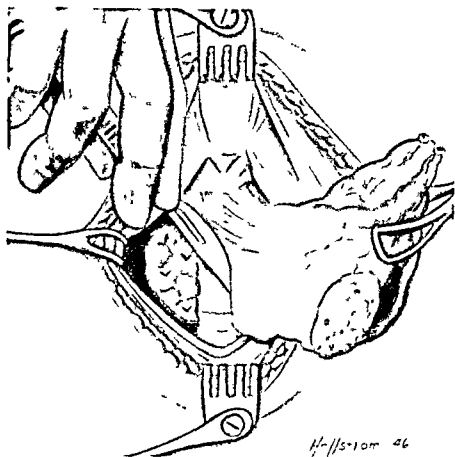


Fig. 67 Stripping right lobe across trachea

trachea is reached a little traction discloses a line of cleavage and dissection of the isthmus is greatly facilitated without damage to the trachea (Fig. 67)

8 After the trachea is crossed traction upon the right lobe and isthmus automatically lifts the left lobe from its bed and in this way

eliminates the trauma which is sometimes required during the effort to raise the left lobe. By this method, it is usually possible to elevate both lobes with thumb forceps only (Figs 68 and 69)

9 After subtotal thyroidectomy, the clamped vessels are ligated individually with No 0 chromic gut. If it is thought necessary, some of the sutures may be anchored. No attempt is made to close over the anatomical capsule of the gland. Instead, the sternothyroid muscle is sutured on either side to the pretracheal fascia with No 00 plain

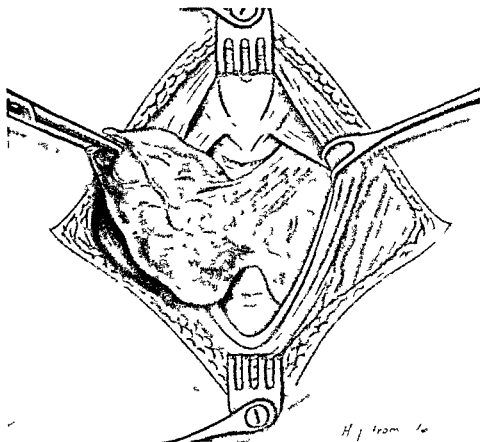


Fig 68 Elevation of left lobe by traction upon right lobe after trachea has been dissected free

catgut (Fig 71). This muscle not only acts as a hemostatic agent controlling any seepage from the gland surface, but prevents the formation of any overlying adhesions to the gland itself as well. Since we have adopted this procedure, we have eliminated drainage in all but

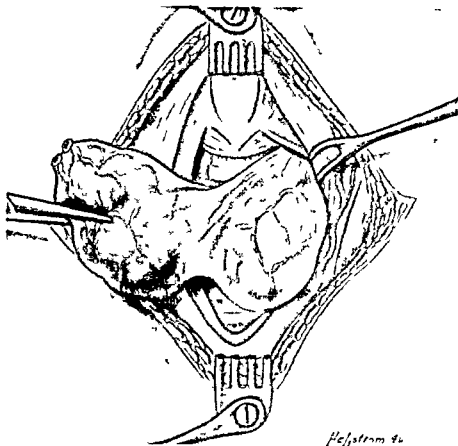


Fig. 69 Further elevation of left lobe by traction on right lobe

the very exceptional case in which a large cavity remains after removal of an intrathoracic goiter

In our last series of 2,000 cases we have not drained thyroidectomy wounds, there being very few exceptions (less than 1 per cent), and have thereby lessened the convalescent period considerably

10 The ribbon muscles are next sutured vertically and the skin is closed with clips, to be removed in 72 hours

The principal accidents to be guarded against are hemorrhage injuries to the parathyroids or to the recurrent laryngeal nerve, collapse of the trachea, and air embolism through the large veins of the neck. In the event of a collapse of the trachea, a tracheotomy must be done instantly. Such accidents can be almost entirely avoided by the adoption of and adherence to a scrupulously careful technique

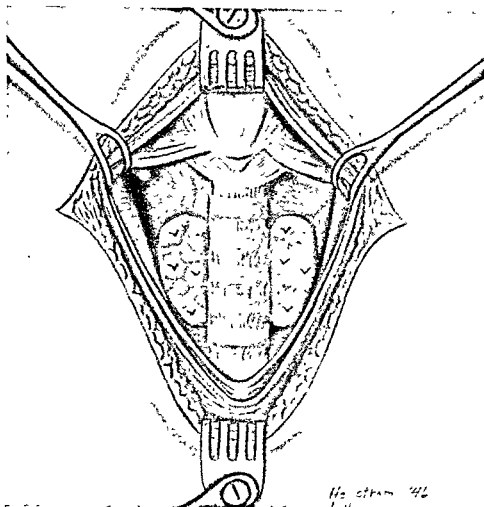


Fig. 70. Remnants of thyroid remaining after removal of both lobes.

AMOUNT OF GLAND TO REMOVE

If too little thyroid tissue is removed in thyrotoxicosis, the disease will persist or recur. Fear of myxedema may make the less experienced surgeon overcautious. It must be remembered that many patients will never be persuaded to undergo a second operation no matter how great the need for it. On the other hand, the removal of an excessive amount of thyroid tissue may be expected to result in myxedema, which may involve personality changes. As revealed by a review of the literature of the past decade, the consensus is that it is the better part of wisdom to run the risk of removing too much rather than too little of the thyroid, because in all probability the gland will undergo sufficient regeneration to prevent myxedematous changes.

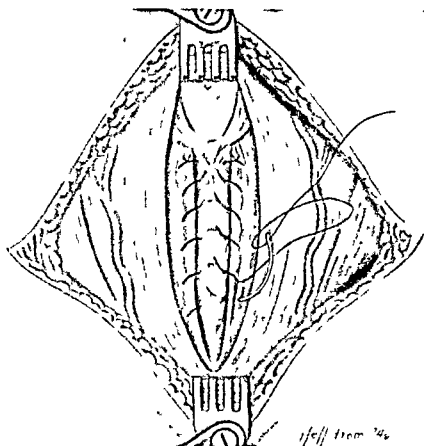


Fig 71 Suture of sterno thyroid muscle to pretracheal fascia

Lahey (1932), who has carefully studied the problem, concluded that a correct decision can be made on the basis of the degree of involution which has been effected by Lugol's solution before operation. In the case of patients in whom the iodine-effected involution of the gland is of high degree, as ascertained by gross appearance of the thyroid (pale, edematous tissue), he would remove relatively less tissue, because the regenerative capacity of such tissue has been reduced to a low level. In patients in whom involution is of low degree, as shown by the brownish red and cellular appearance of the thyroid tissue, he would remove a large quantity, such tissue having a marked capacity for regeneration, if too much is left at operation, the return of excessive thyroid activity becomes highly probable.

According to Pool and Garlock (1934), there seems to be little

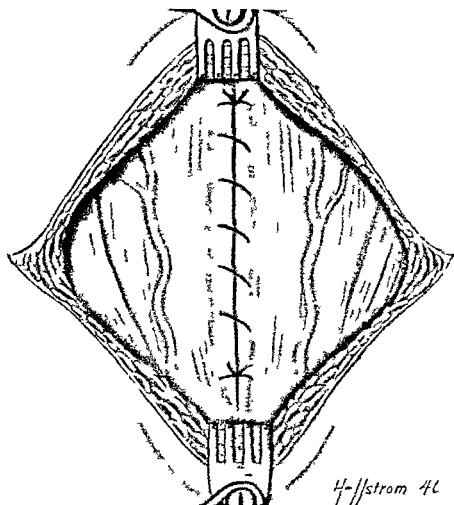


Fig 72 Longitudinal incision sutured

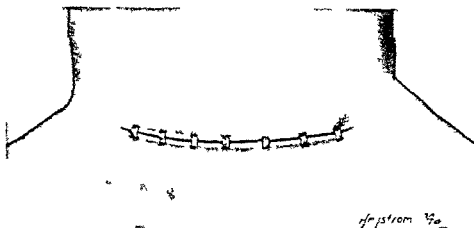


Fig 73 Incision closed

doubt that the occasional thyroid surgeon, not a specialist, will have a high recurrence rate, because of inadequate removal of the gland. He is afraid of injuring the parathyroids and the laryngeal nerve, and in addition he has not yet developed a standard procedure. He may therefore expect many recurrences before he has learned to operate efficiently and adequately in this disease. Pool and Garlock themselves reported a recurrence rate of 9.3 per cent in a series of 171 primary resections.*

Our own conviction is that it is as a rule much better to make sure of removing thyroid tissue in an amount sufficient to prevent a recurrence of the hyperthyroidism than it is to be apparently conservative and so remove too little of the gland. Any degree of hypothyroidism that may result from the removal of an excessive thyroid tissue is readily controlled by the administration of desiccated thyroid at the proper dosage level. Whereas the advent of thiouracil and propylthiouracil may be changing the situation to some extent, surgery still remains the only sure means of permanently relieving hyperthyroidism. This point is worthy of reiteration. It is difficult if not impossible to persuade a patient to undergo a second time a procedure which has already failed to bring relief.

POSSIBLE ERRORS ON THE OPERATING TABLE

The error most frequently made by the less experienced surgeon is the failure to recognize signs of excessive toxicity, as Cole (1941) has pointed out in his recent discussion of the factors determining the mortality rate in operations for thyrotoxicosis. Of course, today patients are given preoperative care that represents a vast improvement on former methods of preparation for operation. Adequate medication with iodine and thiouracil or propylthiouracil will in almost all cases have reduced toxicity to a very low level. The vital reserves will have been increased greatly, and complicating disorders will have been adequately treated. Hence thyroid crisis on the operating table (and postoperatively) has become a rare manifestation. Nevertheless, there still remains the poor risk patient (thyrocardiac or elderly individual) and the patient sensitive to the thio drug. As Cole has remarked: "Information gained about severely toxic patients through many years ex-

* Recurrent hyperthyroidism is discussed at some length in the chapter on "Postoperative Sequelae" page 401.

perience with them should not be cast aside. Although rare, crises do occur, at times without warning and almost always inexplicably.

The pulse rate during anesthesia may give warning of excessive toxicity. If the pulse rate cannot be brought down below 140 with anesthesia, it is advisable to postpone the operation. If the pulse rate rises toward 140 as one lobe is being removed, it will probably be unsafe to attempt the removal of the other lobe. A second stage operation can be performed some weeks later.

Lahey (1941) has warned that many of the fatalities in thyroid ectomy are attributable to the fact that two lobes were removed instead of only one—too much work was done, the surgeon has inflicted too great an operative load on the patient. If before operation the surgeon has decided to remove one lobe only, he should not change his mind no matter how smooth the operative course, surely, the decision to operate in two stages has been reached after careful study of the patient and meticulous weighing of all possible factors.

Another sign indicating that the operative load on the patient is probably excessive is the need for an inordinate amount of oxygen to keep the patient oxygenated, it is the duty of the anesthetist to inform the surgeon of such a difficulty. The condition of the patient then probably is more toxic than the surgeon has had reason to suspect.

As a rule, the attempt to hurry and shorten an operation is unwise except in the case of a severely toxic patient (who perhaps should not have been brought to operation at this time) or in an unexpected emergency arising during the operation. Of course, there is an optimal pace between the extremes of undue haste and excessive slowness.

We have emphasized errors in judgment because they have been shown to be more disastrous than errors in technique. It is assumed that the surgeon will take pains to avoid damage to the recurrent nerve or the parathyroids and to guard against hemorrhage, air embolism, and collapse of the trachea.

UNILATERAL THYROIDECTOMY

In the cases of the thyrocardiac or the patient with a cardiac condition and the elderly patient, a 2 stage operation is usually necessary. Even after many weeks of the most careful preoperative preparation, the patient's condition may not meet the requirements for bilateral thyroidectomy. Such cases are now rendered far less toxic with thion

racil or propylthiouracil than was possible before the introduction of these drugs. Nevertheless, cardiac and elderly patients simply do not have the vital reserves of the younger patient who has no serious complicating disorder, and the surgeon must not subject them to an excessive operative load. A similar situation exists when a patient, as occasionally happens, shows drug sensitivity or fails to respond to preoperative medication.

In the 2 stage operation, the right lobe is removed at the first operation, the isthmus is severed in the midline and the edge is sutured to the pretracheal fascia. Depending upon the condition of the patient from 3 to 6 weeks later the left lobe is removed. The prerequisites for bilateral thyroidectomy (1 stage operation) have already been outlined in the chapter on preoperative considerations (page 315). We would like to emphasize that, whenever there is any doubt concerning the advisability of a 1 stage operation, the surgeon cannot err if he is conservative and performs the thyroidectomy in 2 stages.



Fig. 71. Discrete adenoma.

REMOVAL OF DISCRETE ADENOMAS

The removal of a discrete adenoma is a prophylactic measure against the possibility of eventual malignant degeneration of the tumor tissue. The incision through the skin and platysma is made as in thyroidectomy for exophthalmic goiter (page 344), small bleeders or oozing spots in the skin flap are grasped with small hemostats. Also as in thyroidectomy, care should be taken to cut in the fascial plane between the platysma and fascia on the anterior surface of the ribbon muscles (Fig 59). To avoid severing the cutaneous nerves, the skin flap is not raised laterally more than just enough to make a V between the lateral ends of the incision and the highest point of the midline. If the adenoma has attained unusual proportions, it may be necessary to sever the ribbon muscles, the division should be made high up and as near the larynx as possible, to reduce possible damage to the nerve supply of the upper portion of the muscle. Clamps are placed on the nonadenomatous portion of the thyroid gland above, below, and

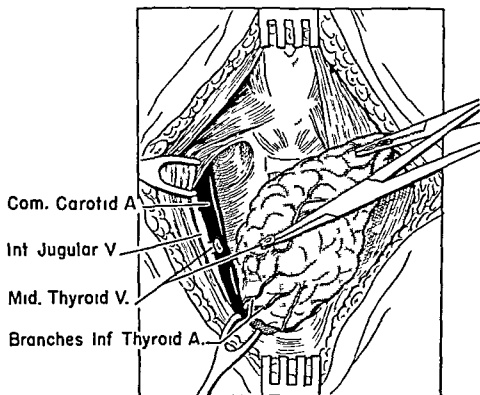


Fig 75 Diagram showing trianguloid depression to be avoided in performing thyroidectomy

along the outer side of the tumor. We have developed and extensively employed a modification of the usual procedure in the placing of these clamps (Fig. 350). To make doubly sure that the clamps in every instance bite into thyroid tissue as we reach the triangularoid depression at the site where the inferior thyroid artery branches to enter the gland

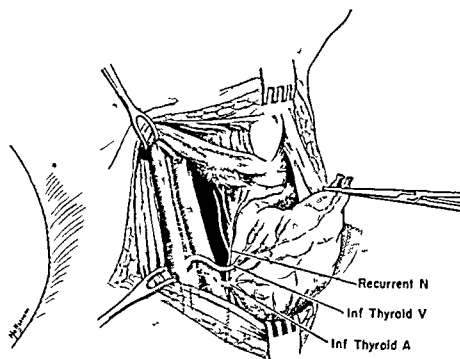


Fig. 76 Diagrammatic drawing showing the portion of the gland which must be avoided in dissection in order not to injure the recurrent laryngeal nerve or parathyroid glands

we place the clamps as described on page 350 under bilateral thyroidectomy. This refinement of technique aids in reducing to a minimum the risk of damage to the recurrent nerve.

The adenoma is excised by cutting through its envelope of thyroid tissue and by careful dissection from the adherent tissue. In carrying out this dissection it must be remembered that in a certain percentage of cases only a thin covering of thyroid tissue may lie between the posterior portion of the tumor and the recurrent laryngeal nerve. In such instances there is considerable danger of damage to the nerve and great care must be exercised in making the dissection. Although

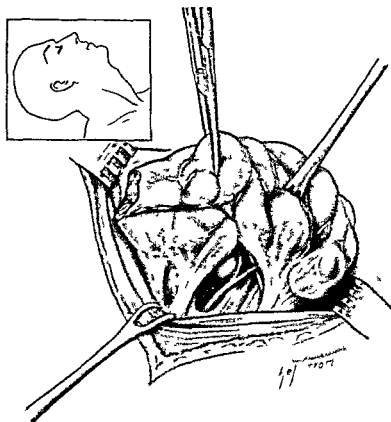


Fig 77 Diagrammatic drawing made at time of operation demonstrating trianguloid area to be avoided during dissection

we do not advise the procedure, some surgeons recommend the routine demonstration of the recurrent laryngeal nerve in all operations for removal of a discrete adenoma. It is to be noted that ligation of the inferior thyroid artery serves to prevent secondary hemorrhage, as in thyroidectomy. When the adenoma has been removed, the affected lobe of the thyroid gland may be reconstructed by suturing the edges together.

If there is any doubt concerning the existence of nodules in the contralateral lobe after exploration by palpation, an exploratory incision into that lobe should be made. Every encapsulated nodule should be removed.

In a considerable number of cases malignant degeneration of a supposedly benign adenoma of the thyroid gland is not diagnosed

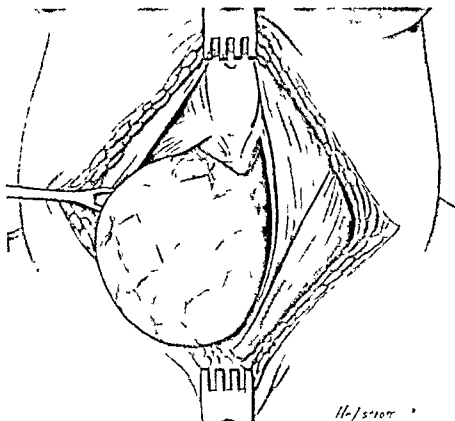


Fig 78 Exposure of discrete adenoma before enucleation

clinically or even at operation. Hence some surgeons urge that, as a routine procedure in the removal of unilateral non toxic adenomas, a lobectomy or subtotal thyroidectomy be done (Ward, 1944, Slaughter, 1946) *

Local recurrent nodules appearing months or years after extirpation of a discrete adenoma should be removed. These cervical masses, as Graham (1938) has demonstrated, are in many cases tumor thrombi frequently encapsulated in the lateral or inferior thyroid veins. Such neoplasms are irresponsive to irradiation, but, following their removal years may elapse before metastasis or local recurrence. These facts make clear the vital importance of extirpation of recurrent nodules. The recurrence of nodules is strong evidence that the primary growth was malignant.

* Other references have been given in the discussion on the pathology of discrete adenomas page 232

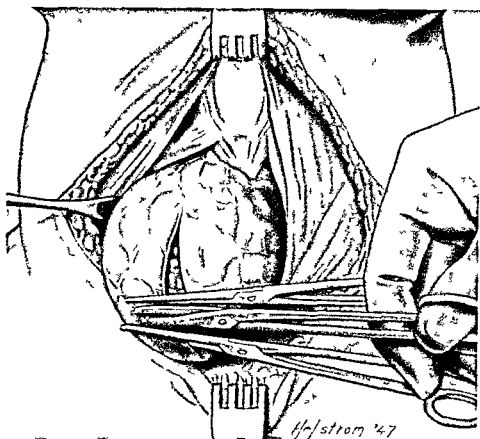


Fig 79 Capsule opened at lower end and enucleation of discrete adenoma begun This dissection is carried around the base of the adenoma

Removal of discrete adenomas is so important a prophylactic procedure that its urgency deserves re emphasis, in the words of Ward (1944) It has been rare to care for a patient with malignant goiter who has not been told at some time by a physician that the goiter was non toxic and harmless, and that nothing should be done about it until signs of the trouble appeared

REMOVAL OF MALIGNANT ADENOMAS

When a benign adenoma undergoes malignant degeneration, at first it invades its capsule, infiltrates into the previously unaffected thyroid tissue surrounding it, and then invades the capsule of the thyroid gland and the blood vessels, especially the veins Invasion of the lymphatics is a relatively late development and as a rule, by the time it occurs, the cancer has become incurable For, in the meantime,

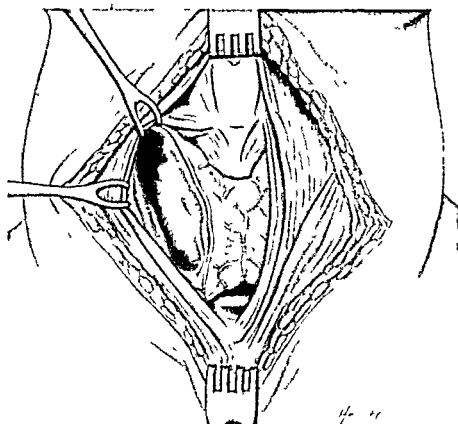


Fig. 80. Enucleation of discrete adenoma completed after which capsule is closed

vital structures contiguous to the thyroid gland have been invaded. In cancer of the thyroid, because of the anatomical relationships of the gland, we often encounter a situation in which a local metastasis can readily be removed whereas much of the primary lesion cannot be, as a result of direct extension of the growth into the trachea, thyroid cartilage, esophagus or common carotid artery. Further, the malignant tissue, having early invaded the venous channels, proliferates within the veins, and disseminates itself to the lungs and bones by way of the blood stream. This great tendency to invade the veins, first stressed by Graham (1924, 1925), has served to guide operative treatment.

It must be remembered that invasion of the venous channels takes place some time before the lesion becomes incurable by surgery (and roentgenotherapy, postoperatively). In many instances, the veins may

have been infiltrated, yet distant metastasis may not have occurred. Then, in such cases, if the neoplasm has not extended its growth through the capsule of the thyroid gland, the prognosis may be regarded as favorable following wide excision of the tumor and its capsule, together with resection of the veins which drain the affected lobe of the thyroid gland. Radical neck dissection will eradicate the most common sites of local recurrence and will often forestall distant metastasis.

Ward (1944) has recommended that, when carcinoma is suspected before operation, a long collar incision be made, slightly higher than is customary. Excision of submandibular extensions may be facilitated by extending one end of the incision upward, in hockey stick fashion. All affected structures, insofar as is possible, should be removed, but, of course, it is essential to preserve both carotid arteries, one recurrent laryngeal nerve, and at least one parathyroid gland.

Usually, the indicated operation includes a radical neck dissection, total hemithyroidectomy on the affected side, removal of the isthmus, and subtotal thyroidectomy on the opposite side, the strap muscles should be removed on the affected side. In some cases the neoplastic growth will have involved or destroyed the recurrent laryngeal nerve on the involved side, more rarely, deliberate sacrifice of the nerve on one side may be necessary — provided, of course, that preoperative examination has shown the other recurrent nerve to be functioning.

Oxygenation during the operation is facilitated and collapse of a trachea which has been weakened by infiltration or pressure may be prevented by the use of an intratracheal catheter with an inflatable cuff.

Dissemination of the malignant tissue by operative manipulation may be avoided by commencing the operation with ligation and resection of the internal jugular vein on the involved side, and low ligation and resection of the inferior thyroid vein. This procedure is definitely indicated when the lateral or inferior veins are found to be thrombosed by tumor tissue.

Lahey (1944), when carcinoma has invaded the parenchyma of the gland after breaking through the capsule of the adenoma, has always made it a practice to do a radical dissection. His procedure includes high and low ligation of the internal jugular vein, after which the sternomastoid muscles are severed high and low. Then, in one block, the following structures are removed: the entire sternomastoid muscle,

tributary veins prethyroid muscles, regional lymph nodes, the isthmus and entire lobe containing the adenoma

As Ward (1911) has remarked mediastinal extension of malignant tissue often proves to be the unsurmountable obstacle to complete removal of the tumor. If there is mediastinal extension of the growth in the form of more or less encapsulated nodules, the suprasternal portions of the tumor may be freed from their bed and from the trachea and used to pull the mediastinal masses through the aperture of the intrathoracic strait

If there is central degeneration within an intrathoracic extension of a malignant adenoma the pseudocapsule may be ruptured by the surgeon who may then evacuate the contents by curette or suction so as to collapse the capsule. Extracapsular finger dissection of the capsule from the superior mediastinum is afterwards carried out

When the intrathoracic extension is hard it may be necessary to split the sternum, but even this measure may prove ineffective when there is extensive infiltration of contiguous structures

Following removal of the tumor lavage with plain sterile water aids the detection of bleeding points and washes out cellular debris. Plain sterile water has a lytic effect on free cancer cells which may possibly be present after operative manipulation of the tumor (Ward 1911)

In the event that diagnosis of malignancy has been satisfactorily established postoperative roentgenotherapy is indicated. Tumors of the papillary group are markedly radiosensitive. Anaplastic large and small cell carcinoma, and carcinosarcoma, on the other hand, are but slightly if at all radioresponsive

REMOVAL OF AN INTRATHORACIC GOITER

Although some intrathoracic goiters attain remarkable proportions (DeCoursey, 1911), in most cases the tumor is small enough to be removed through an ordinary goiter incision so that the bony structure of the thorax need not be disturbed. When the tumor is too large to be delivered intact through the thoracic outlet, most frequently its removal can be effected by opening the capsule of the tumor, breaking down the contents and scooping out the solid or semisolid substance, any fluid being sucked out. It is first necessary, of course, to ligate the blood supply from above. Extracapsular finger dissection usually serves

to free the capsule from its adhesions. Only the gentlest traction is used to lift the capsule from its bed.

Small intrathoracic goiters or adenomas may be delivered as follows. The surgeon dissects free the cervical portion of the thyroid gland, then clamps and divides the superior pole and the isthmus. Afterwards the tracheal attachments are severed. Hemostasis is meticulously maintained and injury to the recurrent laryngeal nerve carefully avoided. After the completion of these preliminary procedures gentle traction upon the cervical portion of the gland eases the intrathoracic growth upward, its delivery being achieved by means of care

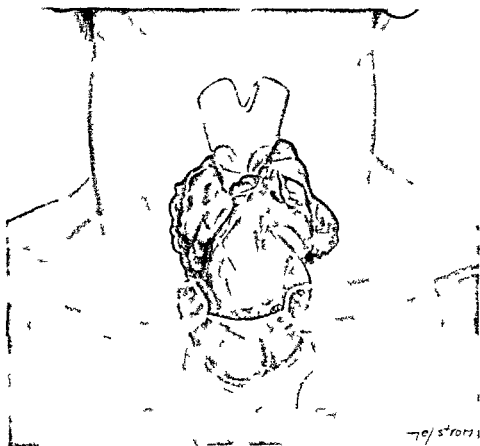
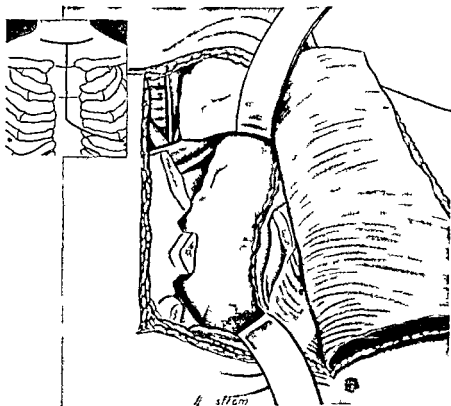


Fig. 81. Intrathoracic goiter should be classified as first, second, or third degree. A—First degree when one third of gland extends intrathoracically. B—Second degree when two thirds extends intrathoracically. C—Third degree when entire gland is intrathoracic. This illustration demonstrates a first degree intrathoracic goiter.

ful dissection. Hemostats are carefully applied as the blood vessels supplying the adenoma are brought into the field.

Except in the rare instances in which there is persistent oozing from the walls of the cavity left after removal of an intrathoracic goiter, few surgeons today pack the cavity with gauze (Guthrie and Schimmel 1944). A survey of the literature shows that the consensus is. Such a procedure increases rather than decreases the probability of infection. Even drainage is usually unnecessary. In most cases intrathoracic pressure soon forces the pleura and mediastinal tissues into the cavity and obliterates it. Packing may lead to the formation of a true cavity which may persist indefinitely.

When drainage is indicated, 2 or 3 small rubber drains may be required for several days or longer. Lahey (1944) in discussing the drainage of deep mediastinal pockets has recommended that the drains be not removed for at least 7 to 8 days and then a rubber or catheter drain should be inserted and gradually shortened during a period of 2



to 3 weeks. In the meantime, the pleura will have expanded and the mediastinal cavity will probably be completely obliterated.

Substernal Approach — Thoracic Approach. In unusual cases, an intrathoracic goiter has attained such a size that it cannot be removed unless by substernal or thoracic approach. The approach may be made through a 'thoracic window' formed by splitting the sternum lengthwise in its middle portion down to the xiphoid and by cutting through the first three ribs, as shown in Fig. 82. We have used the electric circular saw, and chisel and hammer to split the sternum.

It must be emphasized, however, that considerable shock results from such an operation, and the incidence of postoperative complica-

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Fig. 82 Removal of Large Retrosternal Goiter. This operation is designed for the removal of those tumors which are of such large proportions that it would be impossible to deliver them through the superior thoracic strait. Endotracheal anesthesia, with positive pressure if necessary is used.

- 1 A collar incision is made in the usual manner and the flaps dissected upward and downward in the plane between the platysma and the deep fascia.
- 2 An incision is made in the midline, carried to the suprasternal notch and the strap muscles separated.
- 3 The anterior cross communication of the anterior jugular veins is doubly clamped and ligated.
- 4 The strap muscles in the side from which the tumor has developed are incised, transversely and retracted.
- 5 Both the superior and inferior thyroid arteries are ligated.
- 6 A vertical incision is then made in the midsternal line from the collar incision above to the level of the third costal cartilage inferiorly and then extended toward the nipple on the side which the tumor lies.
- 7 The origin of the pectoralis major muscle is incised and the skin fascial — muscular flap thus formed is reflected.
- 8 The second costal cartilage and rib is reflected from the sternum to the anterior axillary line, subperichondrally and subperiosteally.
- 9 The retrosternal and pleural structures are then separated by blunt dissection with the finger introduced above the suprasternal notch from the posterior aspect of the sternum.
- 10 The internal mammary vessels are exposed, doubly ligated and incised.
- 11 With a Gigli saw introduced from the suprasternal notch to the level of the second rib that portion of the manubrium which carried the articulation of the clavicle and the first rib is severed from the remaining portion of the manubrium (see illustration).
- 12 If the tumor is unduly large the third costal cartilage is cut near the sternum. An effort is made to retract the pleura so that it is not opened, if it is opened it is closed immediately. This incision gives adequate exposure to the superior, anterior and middle mediastina.
- 13 Closure is made by layers in the usual manner.

tions is generally high. Unless obstructive symptoms render the operation imperative, it would be wise to forego removal of the tumor in the cases of the elderly patient and the patient with complicating cardiac disorder.

THYROGLOSSAL RESTS

Occasionally, we encounter a cyst, sinus, or tumor, benign or malignant, at any point along the thyroglossal tract in its course from the base of the tongue to the normal location of the thyroid gland. Their origin is from rests of thyroid tissue or from misplaced epithelial cells of the pharynx which have been left in an anomalous situation as the anlage of the gland descended from the foramen cecum (see page 40). A lingual thyroid develops from thyroid tissue remaining at the site of the foramen cecum. When present, the pyramidal lobe is another anomaly arising from a thyroid tissue remnant of the thyroglossal tract. As a routine in thyroidectomy, the surgeon should look for a pyramidal lobe, and if one is found, it should be removed, to diminish the chance of persistent or recurrent hyperthyroidism. In the event that a pyramidal lobe is not excised in an operation for simple goiter, this lobe may later undergo conspicuous enlargement. Before excising other aberrant thyroid tissue in different cases, however, the surgeon should make sure that a normal or nearly normal thyroid gland is present, in exceptional instances, a lingual thyroid or other thyroid tissue anomalously located in the neck may be the only thyroid tissue present.

Contrariwise, when one mass of aberrant thyroid tissue has been found, the presence of others should be suspected. In fact, as a prophylactic measure against recurrence of thyroglossal tumor or cyst, the entire tract from the isthmus to the base of the tongue should be removed. It is to be recalled that generally the thyroglossal tract traverses the midportion of the hyoid bone, complete extirpation of the tract consequently involves the resection of the central portion of the hyoid. Closure of the wound may be facilitated by suture of the divided hyoid, otherwise it need not be sutured.

When the surgical problem is a sinus, its opening should be included in the incision if possible. In the exceptional case, the opening of the sinus is so low that if it were included in the incision, dissection of the suprahyoid portion of the thyroglossal tract through the same incision would be difficult if not impossible, then the incision should

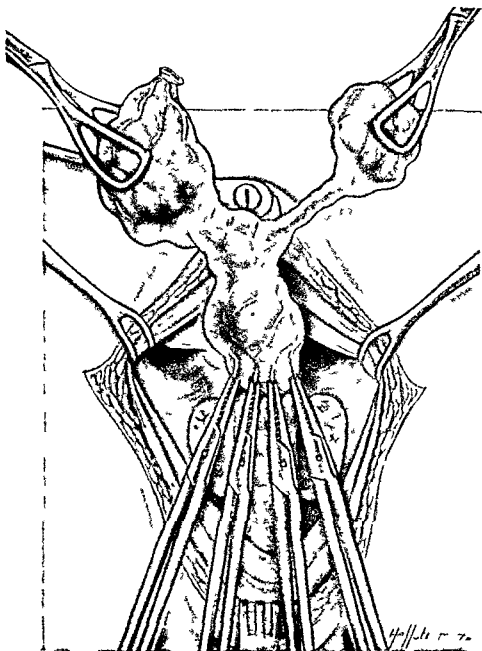


Fig 83 The pyramidal lobes should always be sought for and removed when present. This illustration demonstrates the removal of a large pyramidal lobe.

arteries (DeCourcy, 1923) Previously, ligation of the inferior thyroid arteries was avoided because theoretical considerations rather than clinical experience induced a fear of the possible results. It was thought that patients could not with any degree of safety be subjected to supposedly heroic procedure in which all four thyroid arteries are ligated. Indeed, ligation of all four thyroid arteries within a period of a few weeks does represent an excessively dangerous procedure. Our studies, however, showed the significance of the factor of time, and we were able to develop the following successful routine.

Single or double superior ligation is performed at one sitting, when single ligation is done, the contralateral artery is usually ligated within the week following. The patient is then allowed to return home and is instructed to submit to an almost absolute rest. After 3 or 4 months, the patient is again examined, and if thyroidectomy is still contraindicated, one inferior thyroid artery is ligated. This third ligation, as a

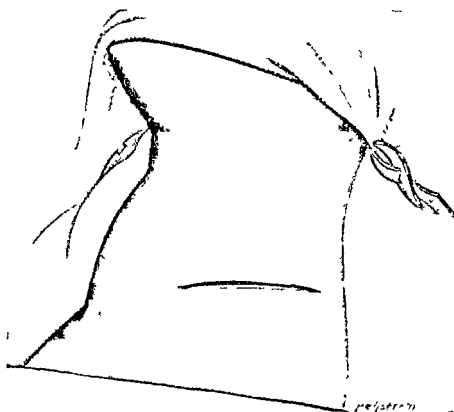


Fig. 85 Ligation of inferior thyroid artery. Position of transverse incision.

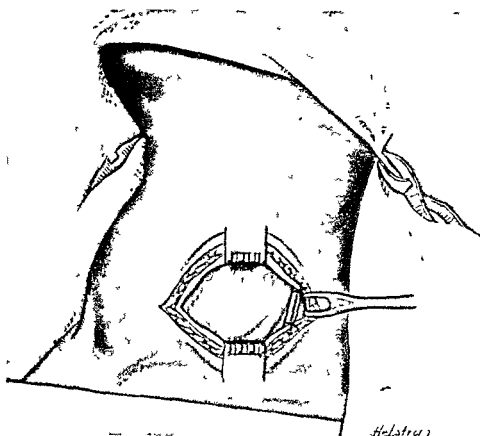


Fig 86 Showing division of deep fascia exposing the muscle fibers and the external jugular vein ligation

rule, results in sufficient reduction of the toxicity to permit a bilateral thyroidectomy. If, however, the patient is still considered a poor operative risk 1 month after the first inferior ligation, then the other inferior thyroid artery is ligated. Thus, the fourth ligation is performed 4 to 5 months after the superior ligations, and, as our experience indicated, this period is sufficient for the development of a slight collateral circulation about the superior poles, so that adverse results do not follow the final ligation.

Our experience with this routine showed that ligation of all 4 thyroid arteries brings about much greater improvement in the patient's condition than does mere bilateral ligation of the superior arteries. Hence the margin of safety at operation is markedly increased. Further, ligation of all 4 arteries greatly diminishes the chance of hemorrhage at operation, and it is rarely, if ever, necessary to allow

the wound to remain open (as was the general practice following thyroidectomy preceded by ligation of only the superior arteries) Finally, *incisions for inferior ligation can be made in the same crease as incision for thyroidectomy and only 1 scar results*

The ligation of 1 or more inferior arteries was performed in many cases with a very low incidence of adverse reactions The following operative technique was employed

A transverse incision is made 2 finger breadths above the clavicle with the center overlying the posterior border of the sternocleidomastoid muscle (Figs 85 and 86) The incision is carried down through the deep fascia until the muscle fibers are exposed (Fig 87) (It is some times necessary to ligate and divide the external jugular vein at the posterior portion of the wound) The sternomastoid muscle is drawn inwardly and the division noted between the thyroid gland and the

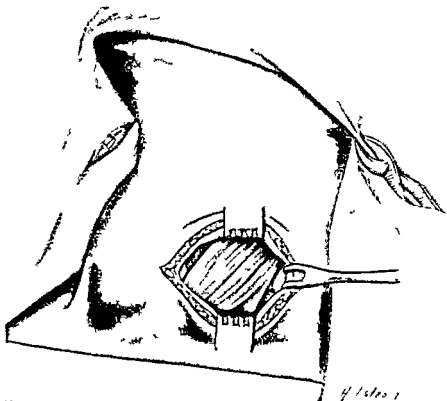


Fig 87 Showing appearance of sterno mastoid muscle before being retracted inwardly

carotid sheath. A hemostat is then placed between the thyroid gland and the carotid sheath, so as to hug the thyroid capsule as closely as possible without opening it, and afterwards the blades are spread apart. The thyroid gland is retracted inward with the sternomastoid muscle and the sheath of the carotid is retracted outward. The scalenus anticus muscle can be seen lying beneath, covered by its fascia. The fascia is opened at the inner margin of the muscle and the inferior thyroid artery can be readily isolated (Fig 88). It is essential that the operative field be kept absolutely dry during the entire procedure, because oozing tends to obscure the landmarks and vital structures may

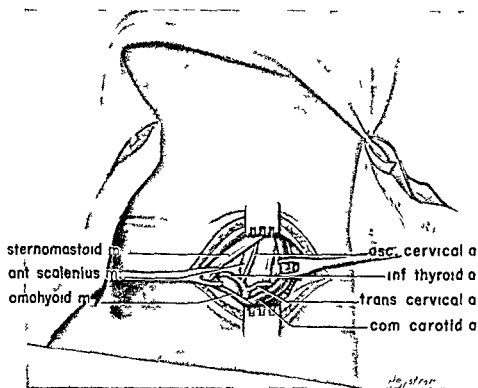


Fig 88 Appearance of field after dissection has been completed, showing ligature of inferior thyroid artery

then be injured. The chief technical dangers are injury to the jugular vein, to the phrenic nerve which lies on the belly of the scalenus anticus muscle, and to the thyroid gland itself. Damage to thyrotoxic thyroid tissue may induce a crisis.

These operations, once almost universally performed as a prelude to thyroidectomy, are of more than passing interest and historical im-

portance. They greatly promoted increase in our understanding of thyrotoxicosis, factors in thyroid crisis, toxic diffuse goiter as differentiated from toxic nodular goiter, abnormal locations and anomalies of important nerves and blood vessels. Modern operative techniques have developed from earlier procedures. And many a finding established in thyroid surgery of more than two decades ago has its direct



Fig. 89 Nodular toxic goiter immediately after removal showing satisfactory removal of superior pole

application. To cite an important illustration, knowledge gained concerning the adverse effects of interference with the blood supply of the parathyroids in certain ligation procedures renders the modern surgeon cautious lest he perform too radical a thyroidectomy. More important still have been the numerous observations concerning the various possible locations of the recurrent laryngeal nerve, the various ways in which it can be injured and injury avoided or repaired, and the results obtained by different approaches. Many surgeons today do not perform a routine demonstration of the nerve because of the dangers of exposure and scar tissue formation — which were early found to be disastrous in what some believe to be an excessive percentage of cases. The surgery of today is based upon past experience and, in its turn, will provide the basis for thyroid surgery of future years.

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CHAPTER XIV

POSTOPERATIVE CARE

IN THE SURGERY of the thyroid gland to a greater extent than in many other fields of surgery, satisfactory results — including a minimum mortality rate — are directly and obviously dependent upon postoperative care. Postoperative vigil must be conscientious and sustained; all measures known to promote the optimal wellbeing of the patient and to aid in the prevention or early detection of possible complications must be thoughtfully taken — and the indicated management of any complication must be instituted without delay. It has been repeatedly shown that as a rule only scrupulous attention to the many vital details of postoperative procedure serves to forestall untoward if not dire developments whose onset may be disturbingly rapid. And good nursing care has a highly beneficial effect on the morale of the patient, especially one who is apprehensive.

CARE IN THE IMMEDIATE POSTOPERATIVE PERIOD

It may be advisable for the anesthetist to see the patient safely in bed after the operation. The patient should be kept prone or flat on one side until he has reacted from the anesthetic. Afterwards, the head of the bed is gradually raised and the patient is kept in a sitting position for the greater part of the immediate postoperative period.

Anoxia must be prevented; not only must the airways be kept free but the patient must be able to breathe easily. All severely toxic patients should receive oxygen therapy. Because of their elevated metabolic rate, the oxygen requirement of such patients is extraordinarily high. As Womack (1910) has pointed out, the mental reaction of the average patient to the sudden discovery that he is in an oxygen tent should be taken into account, if it seems likely that the patient will be placed in the oxygen tent after operation, an effort should be made beforehand to allay possible fears.

During the first 6 hours following thyroidectomy, it is advisable to determine the patient's temperature, pulse rate, and blood pressure

every 30 minutes. Constant watchfulness is necessary to detect severe reactions that may become rapidly fatal.

Very frequently in the early postoperative period, hyperthyroid patients show an increase in pulse rate, and at times the blood pressure also rises. These evidences of increased load on the circulation may persist for some 36 to 48 hours after the operation (or even for 3 or 4 days in unusual cases), but afterwards the load on the circulation generally begins to diminish. At any time postoperatively, however, a marked and continuous rise in pulse rate and blood pressure should suggest some complication, especially anoxemia from laryngeal obstruction—then the early detection of stridor would be vitally important. Thyroid crisis is most likely to occur within the first day or two after operation.

Fluids and glucose in adequate quantities must be supplied beginning as soon as the patient has been returned to bed so that hepatic and renal difficulties may be avoided. Probably 3,000 c c of 5 per cent glucose in saline solution intravenously will be indicated on the day of operation, 500 mg of ascorbic acid and 50 mg of thiamin may be added to the second bottle of glucose solution. Ten per cent solutions of glucose may have an undesirable dehydrating effect.

On the day following the operation, considerable fluid may usually be taken by mouth, the total intake of fluid should be between 3,000 and 5,000 c c. Marked loss of fluid by vomiting or by perspiration (in warm weather) must be taken into account. Renal function must be followed carefully, daily urine output should be at least 1,000 to 1,500 c c. Sulfonamide therapy for any infection of course necessitates an increase in the amount of fluid which the patient must receive.

Sedation. The amount and type of postoperative sedation vary with the individual patient, the degree of his hyperthyroidism, his general condition, and his age. As a rule, it may be inadvisable to administer more medication than is necessary to control pain. The indications for sedation rarely persist beyond the third postoperative day.

Dangers of Oversedation. Inadequate sedation was mentioned by Bayley (1934) as a factor tending to precipitate a thyroid crisis. There is no doubt that some sedation postoperatively as well as preoperatively is essential in all cases. On the other hand, the dangers of oversedation in the hyperthyroid case should be obvious. Sedatives and hypnotics depress respiratory function and tend to cause anoxia. The oxygen re-

quirement is increased in thyrotoxicosis, if only because of the increased rate of metabolism. Such agents are detoxified in the liver—which is almost characteristically in some phase of dysfunction or degeneration in the thyrotoxic patient. McIver and Winter (1943) have demonstrated experimentally the extensive necrosis of the liver as a result of anoxia in the hyperthyroid state. The early symptoms of thyroid storm may be masked by oversedation. A vicious cycle may be set up. As the patient's restlessness and perhaps delirium increase, additional doses of sedative or opiate may be administered, the effect being to increase the intensity of the thyroid storm. Buxton (1944) has warned. There is still present in the minds of many physicians the adage that hypnotics, particularly those of the morphine group, should be given at frequent intervals and by the clock in postoperative thyrotoxicosis.

Anoxia may become an important, often critical, factor in the progress of the patient's disease. In common with Buxton and many other surgeons, we believe that postoperative medication of thyrotoxic patients should be kept at a safe level. And we should not forget that a percentage of patients are hypersensitive to certain sedatives, hypnotics and other drugs.

Iodine Therapy. Iodine therapy is regarded by many as an essential routine following thyroidectomy for hyperthyroidism. Some clinicians continue the administration of iodine until all symptoms of hyperthyroidism have disappeared. Iodine therapy tends to reduce the hyperplasia of the remaining thyroid tissue, which may therefore more rapidly pass into the resting phase. Our routine use of desiccated thyroid beginning 2 weeks after operation for hyperthyroidism is discussed under the heading *Prevention of Recurrent Hyperthyroidism* (page 404).

POSSIBLE POSTOPERATIVE COMPLICATIONS

Nausea and Vomiting. In our experience, when nitrous oxide oxygen mixture is the anesthetic employed and when oversedation (especially with morphine) is avoided preoperatively and postoperatively, most patients are little troubled by nausea and vomiting. In the instances in which vomiting does occur, usually the only measure indicated is the intravenous replacement of the fluid and salts that may be lost. It should be kept in mind, however, that vomiting may be a

symptom which signifies the onset of some serious complication, such as thyroid storm

Hemorrhage The chance of postoperative hemorrhage is almost nil when all oozing in the field of operation has been painstakingly and adequately controlled, as it should be in every case, of course. In the rare instances in which hemorrhage does develop postoperatively, it may be from a large artery and thus cause sudden swelling of the neck and dangerous pressure on the trachea. Breathing may then become exceedingly difficult if not all but impossible, the trachea may even collapse. The consequent stridor, anxiety, and perhaps cyanosis as the hemorrhage develops show the imperative demand for immediate intervention. The necessity for speed on the part of the physician available under these conditions has been dramatically expressed by Lahey (1944). Certainly there must be no delay in opening the wound—otherwise the patient may die forthwith in his bed. Once the obstruction to the airway has been removed by emergency measures and after the patient has been transported to the operating room, usually the bleeding vessel or vessels may be readily identified and the main trunk easily ligated. In some cases it may be necessary to ligate both superior and inferior thyroid arteries to control the bleeding. It has been stated that such hemorrhages are most likely to occur one to ten hours postoperatively.

In other instances there may be slow bleeding from a small vessel or a capillary ooze, and so, exceptionally, a hematoma may appear under the skin flap 2 to 4 (or perhaps more) days after operation. There may be no interference with breathing. Opinions differ as to the advisability of operative evacuation by a second operation or of waiting for the liquefaction of the hematoma and subsequent external drainage (which may necessitate frequent changes of dressing).

A few days after operation, serum may accumulate under the skin flap. A previous hematoma may lead to the collection of serum, but more often the accumulation of serum is a result of trauma or the use of the larger sizes catgut. Fine catgut in the deep ties is less likely to favor collection of serum, because the finer the suture the more readily it is absorbed, other factors remaining the same. The serum may be aspirated after the introduction of a needle through the incision.

Infection Infection beneath the skin flap is of very rare occur

rence In many cases it may be simply controlled, as by the application of hot packs to the neck, flaxseed poultices are recommended by some At times it may be necessary to probe for purulent fluid, exceptionally, there may be a collection of deep pus If fluctuation is observed, opening of the incision and drainage are indicated Marked elevation of the temperature and intensifying extension of the infection will necessitate chemotherapy, usually either with the appropriate sulfonamide or with penicillin Culture and identification of the organism will of course guide therapy It must be remembered that any infection causes a rise in the metabolic rate and therefore places a further strain on the thyrotoxic patient Severe infections may require the use of the oxygen tent It is of the utmost importance that sufficient fluid be supplied daily, orally, or intravenously

Removal of an intrathoracic goiter may most exceptionally be followed by an infection which extends into the mediastinum Still more rarely, mediastinal infection may occur after other types of operation on the thyroid gland We encounter the usual symptoms of infection and, besides, we would expect roentgenograms to show a widening of the mediastinum Under such circumstances the mediastinum should be drained at once, and sulfonamide or penicillin therapy promptly instituted

Hepatic Difficulties As is well known, hepatic damage is a very frequent if not an invariable accompaniment (or result) of hyperthyroidism (see page 136), and accentuation of this difficulty must be avoided insofar as is possible by providing adequate amounts of intravenous glucose in the early postoperative period and of course, when otherwise indicated The occasional patient with jaundice should not only receive intravenous glucose in plentiful supply but also have a diet high in carbohydrate, protein and vitamins

Congestive Heart Failure When the load on the circulation has been increased (as it often is), after thyroidectomy and when the patient is elderly or has a complicating cardiac condition, signs of congestive heart failure may appear Exceptionally congestive heart failure may be seen in the younger patient with no history of previous circulatory trouble Thyrocardiacs or potential thyrocardiacs should be spared all unnecessary strains upon the heart and should have special nursing care, under certain conditions the administration of oxygen (or oxygen and helium) becomes necessary The forcing of intravenous

fluids is absolutely contraindicated in these cases it may lead to respiratory distress or even paroxysmal dyspnea. The elderly patient or thyrocardiac should be examined before he receives intravenous fluid and should be carefully watched while it is being administered.

Auricular Fibrillation and Auricular Flutter As a rule, when auricular fibrillation has resulted from hyperthyroidism, adequate treatment of the thyroid disorder will cause the disappearance of the auricular fibrillation. Digitalization preoperatively is a preventive measure directed at practically certain return of auricular fibrillation postoperatively in patients with this cardiac difficulty. For a lengthy period following the operation, digitalis alone is indicated as the medication whose purpose is the restoration of the normal rhythm.

Patients with a previously normal heart rhythm rarely have attacks of auricular fibrillation postoperatively unless they are more than 40 years of age and unless the load upon the circulation is high. Transient attacks of auricular fibrillation during the preoperative period signify the probability that such attacks will occur after operation. Preoperative digitalization is indicated. Digitalization before operation may be necessary also in cases in which the rhythm is normal but in which there is some serious cardiac condition.

When auricular fibrillation does appear in a patient after an operation on the thyroid, not only should digitalization be carefully carried out with due regard for individual tolerance but also all possible measures should be taken to ensure the maximum degree of comfort — and of course, watchfulness is in order. Overdigitalization must be avoided, for otherwise there may ensue distressing if not serious symptoms. When auricular flutter occurs postoperatively, as it does in a percentage of cases, the treatment and general management of the patient are the same as for auricular fibrillation.

Collection of Mucus Collection of mucus may follow trauma to the upper respiratory tract as a result of the use of pharyngeal airways and nasopharyngeal or endotracheal tubes. Also, a patient whose trachea has been deviated by pressure may experience difficulty in raising mucus. In still other cases, fluid may collect in the tracheobronchial tree because of regurgitation, as when the stomach is distended. Tracheal aspiration or bronchoscopy is indicated when the patient cannot raise mucus by coughing.

Injury to the Recurrent Laryngeal Nerves Adequate precautions

and suitable surgical technique during an operation on the thyroid gland render extremely unlikely any injury to either of the recurrent laryngeal nerves. When one recurrent nerve is injured the patient's voice may be affected temporarily or permanently, but laryngeal obstruction will in all probability not ensue and no special treatment is to be recommended.

Extremely serious results follow injury to both recurrent laryngeal nerves. Obviously the surgeon should take every possible measure to prevent such an eventuality. The first symptoms of bilateral injury may be sudden marked stridor and cyanosis which are caused by bilateral cord paralysis and laryngeal obstruction; then a tracheotomy must be performed immediately. Clute and his collaborators (1944) have remarked: "The surgeon's great tendency in the presence of marked stridor is to delay tracheotomy too long; Men still say that when cyanosis appears a tracheotomy must be done." This policy of waiting for cyanosis before doing a tracheotomy will result in some fatalities because the margin of safety in partial tracheal obstruction is very low.

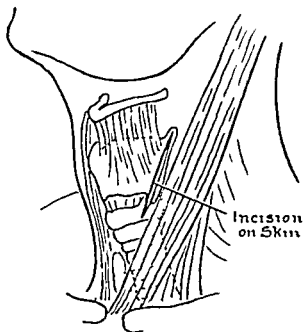


Fig. 90 Placement of the cutaneous incision on (From Woodman DeGraaf *Archives of Otolaryngology* 43 63 65 1946)

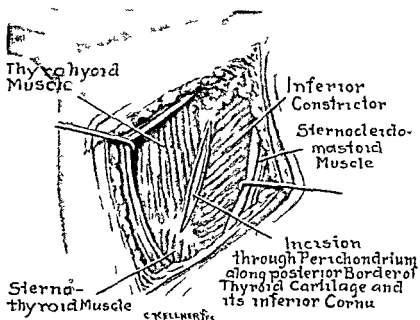


Fig 91 An incision has been made along the posterior border of the lateral thyroid cartilage and the inferior cornu down to and through the perichondrium (From Woodman DeGraaf *Archives of Otolaryngology* 43 63 65 1946)

and any slight increase in the obstruction may at once produce a fatality. Following tracheotomy, radical treatment of the paralyzed cords may be postponed for several months and meanwhile there is the chance that breathing will improve. Seldom however, does one of the cords regain its motility and it may be advisable to perform a radical operation, such as enlargement of the glottic opening by transplantation of the omohyoid muscle to the base of one arytenoid cartilage and reconstruction of the larynx (King, 1939), or bilateral submucous resection of the cords (Hoover, 1940).

Other Causes of Laryngeal or Tracheal Obstruction Injury to the fine muscles of the larynx, spasm of the tracheal muscles or edema of the false cords as well as bilateral injury to the recurrent laryngeal nerves may cause pronounced obstruction of the larynx or trachea with resultant marked stridor. (The problem of hemorrhage and pressure on the trachea has been discussed on page 385.) Whenever the obstruction interferes seriously with breathing tracheotomy must be done. At times, patients with glottic obstruction from edema or cord paralysis

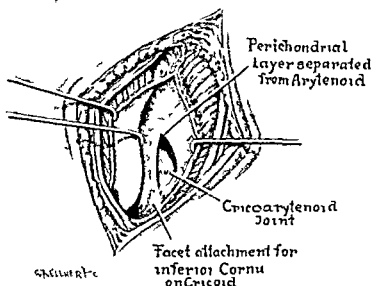


Fig 9² The perichondrium has been separated from the arytenoid (From Woodman DeGraf *Archives of Otolaryngology* 43 63 65 1916)

will be found to have areas of atelectasis the mucus is not coughed up and collects in the tracheobronchial tree to block the air passages

THYROID CRISIS

The last 2 decades have witnessed a great reduction in the incidence of the syndrome known as thyroid crisis or thyroid storm, featured by rising pulse rate and temperature, restlessness vomiting, emotional excitement, and sometimes delirium, mania and coma. The great decrease in the frequency with which we encounter this reaction must be attributed to improved preoperative and postoperative care, optimal timing of the operation, special treatment of the elderly and poor risk patients and improved methods in iodination and perhaps thiouracilization. Nevertheless, despite the application of what are believed to be the wisest measures, clinicians still encounter thyroid crisis in a certain percentage of patients. The explanation of this fact may depend upon the future elucidation of the basic cause or causes of such severe reactions.

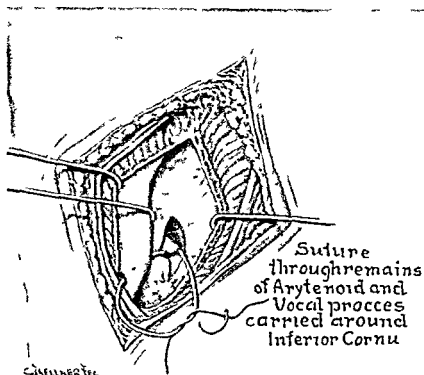


Fig 93 Most of the arytenoid has been removed. Chromic gut has been carried around the vocal process so that the cord may be drawn laterally and sutured to the inferior cornu of the thyroid cartilage (From Woodman DeGraaf *Archives of Otolaryngology* 43 63 65 1946)

Bayley (1934) and Ransom and Bayley (1934) in their study of the preoperative and postoperative factors in fatally terminating thyroid crisis pointed out that a preoperative crisis may be precipitated by (1) delay in admitting toxic patients to the hospital, (2) surgical procedures not directed at control of the thyrotoxic condition, (3) infections of many types, (4) various minor diagnostic and therapeutic procedures, (5) inadequate sedation. Special stress was placed upon the factor of adequate sleep, and Bayley stated that many thyrotoxic patients do not receive sedatives in sufficiently high dosage to ensure the needed rest. Nevertheless there is enough evidence at hand to convince us that oversedation is highly dangerous and may be the precipitating factor in a percentage of thyroid crises. At all times in the management of the thyrotoxic patient, the problem of sedation is difficult and involves vital considerations.

The most striking symptoms in thyroid crisis are those arising as a result of disturbances within the central nervous system at first, euphoria, talkativeness, emotional outbursts, fixations, and later, delirium, mania, coma. Many observers are in agreement that these symptoms are caused chiefly by increasingly severe deprivation of oxygen. A number of investigations have provided evidence in favor of this theory. Cohen and Gerard (1937), and other workers, have demonstrated in experiments on animals that thyroid hormone increases the respiration of tissues *in vitro*. Moreover, the oxygen consumption of brain tissue from hyperthyroid animals is about four times that of brain tissue from normal animals. The absolute concentration of certain enzyme systems is much greater in brains of hyperthyroid animals than in brains of normal animals, certain dehydrogenases being increased relatively more than certain oxidases. Kessler and Gellhorn (1942) used the electroencephalograph to study the effect of anoxia on brain potentials of hyperthyroid animals, they found that the administration of desiccated thyroid signally accentuates the sensitivity of unanesthetized animals to reduced oxygen pressure.

Maddock, Collier and Pedersen (1936) determined the concentration of epinephrine like substances in the blood of hyperthyroid patients. The peripheral venous blood of the majority of patients who were responding well to preoperative treatment did not contain such substances in detectable amounts. Low concentrations of epinephrine like substances were occasionally present in the blood of patients whose progress was unsatisfactory and who had fever. Postoperatively, some patients were found to have low level of epinephrine or some related amine(s) in their peripheral venous blood, 2 patients in severe thyroid crisis showed the highest concentrations. One patient recovered from the crisis and, at about the time of recovery, the test for epinephrine like substance became negative.

Perazzo (1931) observed that moderate doses of epinephrine may be followed by markedly advanced fatty degeneration of the liver. Thus, the problem of the relationship of sympathomimetic substances, thyroid dysfunction and liver damage (see Chapter VIA, page 133) is raised. Additional complications in the way of clear interpretation of the many convergent and divergent lines of investigation of thyroid storm arise from the observations which have proved the increased need

for oxygen in the tissues of the thyrotoxic patient and have indicated some of the results of oxygen lack in hyperthyroidism. The myocardium and the adrenal medulla as well as the liver are affected by oxygen deficiency, which has its most readily observed effects on the central nervous system.

The possible significance of sympathomimetic amines in thyroid crisis has been set forth by observations along several different lines. The administration of epinephrine or a related catechol to experimental animals has been shown to result in the reproduction of the chief features of myocardial disease. Raab (1943) and other investigators have suggested that increased production of epinephrine like substances may be the cause of the arrhythmia and the myocardial dilation, hypertrophy and degeneration observed in thyrotoxic patients. Raab reported that the majority of hearts in a series of patients who died from cardiac failure contained abnormally high concentrations of epinephrine and sympathin or epinephrine like catechols. Large doses of thyroxin increase the concentration of such substances in the hearts of animals. A deficiency of thiamin has the same effect, thiamin requirements, as is well known, are greater in hyperthyroid individuals than in normal persons. Additional observations which strongly support the theory that the thyroid gland and the adrenals have synergistic actions have been discussed in another section (page 274), and the conclusion was reached that most of the symptoms of thyrotoxicosis may result from an imbalance of the sympathetic nervous system, some circulating sympathomimetic toxin being the cause of the imbalance. Factors stimulating the adrenals are physical and psychic trauma, emotional stresses, asphyxia, infections, hemorrhage, unusual exertion, such factors also may precipitate thyroid disorders.

Recently, Buxton (1944) has examined the evidence that thyroid crisis is not a specific entity and that death in this state results from the various complications associated with the augmented metabolism which are often injudiciously and inaccurately treated. After an overall survey of the frequently reported cases, Buxton came to the conclusion that there seem to be two outstanding clinical features common to all such cases. (1) a progressive exacerbation of all the symptoms of thyrotoxicosis which indicate disturbances of function in each of the great body systems, particularly the hepatic, renal, cardiovascular and

central nervous systems, and (2) a breakdown in one or more of these systems, as evidenced by terminal clinical signs and symptoms and by the necropsy findings. Buxton perceived no uniformity of findings and no pathognomonic features common to all cases, and stated: 'It is our belief that there are all gradations of response to increased amounts of circulating thyroid hormone and that thyroid crisis is an extreme response, differing only quantitatively from reactions of lesser degree and initiated or augmented and often brought to a fatal outcome by intercurrent complicating factors.' With this theory in mind, Buxton reviewed a series of cases of thyroid crisis observed at the University of Michigan Hospital from 1934 to 1943. More than 50 per cent of these patients had died in thyroid crisis. The majority were between the ages of 40 and 70 years. The records showed that in these cases the ratio of toxic adenomatous goiter to a diffuse toxic goiter was 2:1. With regard to the fatalities, Buxton believed that death could have been attributed to 1 or more of the following factors: diabetes mellitus with coma, pulmonary edema and congestion, atelectasis, pneumonia, oversedation, overdigitalization, cardiac failure, hepatitis and cirrhosis, wound infection, septicemia. The adverse effects of oversedation particularly impressed Buxton. In several cases, hypnotics evidently caused anoxia. Further, in the instances in which there was apparently no oversedation, other causes of reduced intake of oxygen were indicated by the records of these patients: a considerable percentage of whom had pulmonary or cardiac difficulties. The cases of severe wound infection and septicemia obviously were erroneously classified as thyroid crisis. Buxton thought that the evidence from the records of these cases of thyroid crisis confirmed his contention.

The profound symptom complex designated as thyroid crisis supervenes only in those patients in whom there is a break in the chemical and physiologic compensatory processes of the individual. Such a breakdown, Buxton emphasized, may result from infections, minor diagnostic and therapeutic procedures, and unwise surgical procedures. It is our opinion that Buxton's report, although it may not contribute directly to the ultimate solution of the problem of the causative factors in thyroid crisis, definitely points out once again the vital importance of painstaking preoperative, operative and postoperative management of the thyrotoxic individual. The body systems of the hyperthyroid patient are hypersensitive — probably in several different ways — and

the reaction to injudicious procedures may spell the precipitation of a crisis, whether or not termed a 'thyroid crisis'

Treatment Sedation is generally necessary to control the emotional and muscular symptoms, but oversedation must be avoided. Heavy dosage with morphine must be expected to lead to anoxia, soluble barbitol compounds may be administered subcutaneously along with the morphine so that the dosage of the latter may be reduced. Because of the greatly increased rate of metabolism and the increased need for oxygen in thyroid crisis, it may be necessary to keep the patient in the oxygen tent for many hours to several days, according to the patient's condition. Fluids must be abundantly supplied — in many cases as much as 5,000 c.c. daily. Some authorities recommend that intravenous instillations of 5 per cent glucose in normal saline solution be alternated with 5 per cent glucose in distilled water when it is not otherwise possible to maintain urinary output at the desired level of 1,000 to 1,500 c.c. per day. But care must be taken not to put an excessive load on the circulatory system, especially in the case of the thyrocardiac or the elderly. Sodium iodide may be administered intravenously in doses up to 1 Gm. once or twice daily. The patient's room should be cool, an air conditioned room being used if possible during warm weather.

PARATHYROID TETANY

Improvement in the techniques of thyroid surgery and a more precise knowledge of the frequent aberration as well as the usual anatomic location of the parathyroid glands have brought about a reduction in the incidence of postoperative parathyroid tetany so that it is now a rare complication. In 1937, Swinton stated that the incidence of this condition was no greater than 1.5 per cent in some large clinics and as low as 0.5 per cent in others.

Parathyroid tetany may be caused by removal of sufficient parathyroid tissue to diminish markedly the secretion of parathyroid hormone, or by interference with the blood supply to these glands. In the immediate postoperative period, edema may be accompanied by a transient tetany, which is probably a result of ischemia and which disappears with the subsidence of the edema. Some time after thyroidectomy, thrombosis or fibrosis may obstruct the circulation to the parathyroid glands and so give rise to tetany. When the damage to the para

thyroid tissue is extensive or when much tissue has been removed, tetany may occur within a matter of hours after an operation on the thyroid gland

When, as a result of parathyroid deficiency, the blood calcium has fallen to 7 or 8 mg per cent, a condition of latent tetany exists, an attack being probable after unusual exertion, emotional stress, menstruation, or overbreathing

A drop in serum calcium to a level between 4 and 6 mg per cent generally gives rise to the typical signs and symptoms of parathyroid tetany. Carpopedal spasm is often the first symptom. Other muscular contractions invariably occur, and the slightest stimulus may induce violent spasms of facial and abdominal muscles. There may be constant numbness and tingling of the feet, legs, hands and face. Epileptiform convulsions may occur. The onset of postoperative tetany may be sudden and the violent muscular contractions may interfere seriously with breathing and swallowing. Spasm of the glottis or diaphragm may cause death unless intervention is prompt and effective.

The acute spasms may be controlled within a very few minutes by the intravenous administration of from 5 to 10 c c of 10 per cent calcium chloride solution mixed with 100 c c of normal saline solution to prevent sloughing. Sloughing will result if leakage occurs outside the vein. Calcium gluconate is less irritating to tissues but less effective than calcium chloride. Doses of 10 to 20 c c of 10 per cent calcium gluconate solution may be given intravenously or deep intramuscularly into the buttock.

Following such an injection, the serum calcium rises temporarily, only to sink to its former low level within one to four hours. The injection may have to be repeated once or twice. Immediately after the first injection of calcium, parathyroid extract (1 to 3 c c of the extract which contains 100 U.S.P. units per c c) should be given intramuscularly or intravenously. After several hours, parathyroid extract begins to manifest its effect by maintaining the serum calcium at a level above that at which the attack occurred.

In severe hypoparathyroidism, injections of parathyroid extract must be made daily because the effect wears off within 20 to 24 hours. Not only is the extract costly but also a tolerance to its action develops gradually until even large doses are ineffective in maintaining serum calcium at the necessary level to prevent tetany.

In the treatment of both transient and chronic hypoparathyroidism, a high calcium intake is essential. From 10 to 15 Gm of calcium lactate or calcium gluconate and a quart of milk daily constitute an adequate supply of calcium. To promote utilization of the calcium ingested and to maintain serum calcium at the normal level in hypoparathyroidism, dihydrotachysterol, a congener of vitamin D is at present generally prescribed in the form of capsules (each of which contains 0.625 mg of the active substance). The dosage depends upon the intake of calcium and upon the severity of the hypoparathyroid condition. MacBryde (1944) found that, in severe chronic hypoparathyroidism, 1 or 2 capsules of dihydrotachysterol a day may be sufficient to maintain serum calcium at the normal level, provided 10 to 15 Gm of calcium lactate powder was also administered daily. It is to be noted that large doses of dihydrotachysterol may cause hypercalcemia and severe toxic effects. In chronic cases, the maintenance dose is determined by repeated estimations of serum calcium, and should be the minimum necessary to maintain a normal concentration of calcium in the blood. Large doses of vitamin D gives results similar to those obtainable with dihydrotachysterol. The vitamin may also cause hypercalcemia and associated toxic effects.

The possibility of latent parathyroid tetany or mild chronic hypoparathyroidism as a complication following operations on the thyroid gland should be considered because of the degenerative changes which eventually take place as the serum calcium remains subnormal for a prolonged period. The most serious late development in most cases is the formation of bilateral cataracts. Occasionally, the inorganic phosphate of the blood may rise, and severe renal damage may ensue. Other symptoms of chronic hypoparathyroidism are gastro-intestinal disturbances (flatulence, alternating constipation and diarrhea), loss of hair, ridging of nails and horizontal grooving of teeth, muscular spasm in arms or legs following slight pressure or moderate physical exertion. Diagnosis depends upon determination of the serum calcium and upon confirmatory evidence afforded by the following signs: *Chrostek's sign* gentle tapping over the trunk of the facial nerve and just anterior to external auditory meatus will cause spasm of the innervated muscles. *Erb's sign* a comparatively weak electrical stimulus of a motor nerve causes muscular contraction. *Trousseau's sign* carpal spasm occurs within one to three minutes after inflation of the blood

pressure cuff applied above the elbow, the muscular contraction results from temporary deprivation of the blood supply to the nerve trunk.

Although desiccated thyroid promotes absorption of calcium and is a factor in the maintenance of a normal level of serum calcium in hypothyroidism the possibly untoward effects of administration of this substance to the (formerly) thyrotoxic patient with hypoparathyroidism should be carefully taken into account — an undesirable reaction may follow its use even when hypothyroidism and hypoparathyroidism co-exist as postoperative complications.

We always leave sufficient thyroid tissue at the posterior portion of the gland so that subsequent scar tissue formation does not jeopardize the parathyroid glands (or recurrent nerves). On rare occasions in our experience, a temporary tetany has occurred within 24 to 48 hours following thyroidectomy. This condition was probably the result of edema of the parathyroids and responded well to calcium therapy usually disappearing within 12 hours.

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CHAPTER XV

POSTOPERATIVE SEQUELAE

IT IS OUR conviction that all patients who have undergone thyroidectomy require frequent examination by one who understands thyroid manifestations and can determine to what extent the operation has been a success. When the patient has received optimal preoperative and postoperative care, and when the operation has been timed with nicety and skillfully done, the incidence of late complications is low. The great majority of patients who have been subjected to thyroidectomy for thyrotoxicosis do eminently well and remain free from a recurrence of their previous condition and are untroubled by hypothyroidism, progressive exophthalmos or other potentially dangerous developments. Nevertheless, in certain percentage of cases, complications do eventuate and, unless treated early and adequately, may have serious or even fatal results. The importance of proper postoperative management is so great, that if the operation and its follow up treatment can remain in the hands of the same surgeon for months or years if necessary, the benefit to the patient is almost immeasurable. Unfortunately, such an arrangement is seldom feasible. Regular examination is obviously indispensable and may frequently be life saving in the cases of thyrocardiacs, the elderly, and those showing pronounced exophthalmos.

POSTOPERATIVE HYPOTHYROIDISM

The incidence of hypothyroidism following thyroidectomy is very low when the operation has been skillfully performed in cases in which a condition of true hyperthyroidism actually existed. The precise incidence of hypothyroidism following thyroidectomy is difficult to determine not only do varying degrees of hypothyroidism occur but also the diagnosis of this postoperative complication is not always as simple as it is commonly stated to be. Nafe (1940) recognized 3 types of hypothyroid patients in 300 cases reviewed by him. (1) patients who were definitely myxedematous, requiring more or less continuous medication with desiccated thyroid—1 per cent of cases in this series,

(2) patients with definite hypothyroidism — which, however, disappeared after a period of several months, little or no medication being given — approximately 6 per cent of cases, (3) patients with rather indefinite symptoms of hypothyroidism (lack of energy, general malaise, inability to work), the condition improving markedly following medication with small doses of desiccated thyroid. The incidence of such borderline hypothyroidism was not stated by Nafe and may be difficult to determine. The frequency of occurrence of postoperative hyperthyroidism is much higher after thyroidectomy for diffuse goiter with hyperthyroidism than after thyroidectomy for nodular goiter.

As a late complication of thyroidectomy, hypothyroidism seldom appears before the second or third month after operation. The degree of hypothyroidism is not directly dependent upon the amount of remaining thyroid tissue. The most significant factors concerned appear to be (1) activity of the remnant (i.e., extent of functional capacity), and (2) ability of the remaining thyroid tissue to increase its activity, assume its function, or undergo regeneration following thyroidectomy.

Diagnosis may of course be suggested by the typical symptoms of myxedema — such as marked gain in weight, lack of energy, sallow color, dry skin with thickening and scaling on dorsum of hands, and puffiness of eyelids. Characteristically, but not invariably, there is a reduction in the basal metabolic rate, most cases of myxedema showing readings of between — 20 and — 40. In many cases however, the basal metabolic rate may be close to normal. Blood cholesterol is as a rule above normal. The diagnosis suggested by the clinical picture, the basal metabolic rate and blood cholesterol may be confirmed by a therapeutic test with small doses of thyroid extract.

It must be emphasized that most cases of hypothyroidism following thyroidectomy will undergo improvement without medication and also that generally the remnant of thyroid tissue will resume its normal function more readily when desiccated thyroid is not given. Obviously, however, no case of marked hypothyroidism should be allowed to go untreated.

RECURRENT OR PERSISTENT HYPERTHYROIDISM

The recurrence of hyperthyroidism after thyroidectomy is an extremely unpleasant and undesirable experience for both the patient and the surgeon. Yet it is an experience which still seems to occur with

unwarranted frequency, even though much progress has been made during recent years toward reducing the incidence of such recurrences.

As Thompson, Morris, and Thompson (1930) have stressed, the frequency with which recurrent hyperthyroidism is encountered depends in some measure upon how carefully the patients are followed and how well their postoperative course is interpreted. It may be expected that the longer and more carefully a group of patients is followed, the higher will be the rate of recurrence* — simply because more of the later appearing cases will be seen and diagnosed. In a more recent comprehensive study, Preston and Thompson (1942) distinguished carefully between persistent and recurrent hyperthyroidism. In common with other authors they considered the thyrotoxicosis to be persistent when there was evidence that the disease had not temporarily disappeared after the operation, unless iodine had been administered, the hyperthyroidism was regarded as recurrent only when there was evidence to show that, after operation, there had been a period in which the disease was not present, no medication being given at the time. The incidence of recurrent hyperthyroidism as reported by various authors is given in the following table.

It is to be noted that in general the reports in the literature do not distinguish between persistence and recurrence of the disease when the incidence of postoperative thyrotoxicosis is given. Nevertheless, according to Preston and Thompson (1942), there seems to be general agreement that all patients having subtotal thyroidectomy for toxic goiter, 2.7 to 6.5 per cent have severe enough postoperative thyrotoxicosis to require a second thyroidectomy. As shown by our own experience, however, it is possible to reduce the incidence of postoperative thyrotoxicosis to less than 1 per cent in a large series of patients (DeCourcy, 1941, 1942), the factors involved are discussed in a later section in this chapter (page 405).

Causes. Authorities are in general agreement that the outstanding cause of persistent and recurrent thyrotoxicosis is the failure to remove enough thyroid tissue. In general, the greater the amount of thyroid tissue left at operation, the greater the probability of persistence or recurrence of hyperthyroidism, and, conversely, the more

* Here we are assuming that the patients all receive the same postoperative care. Of course the better the postoperative management the lower will be the incidence of recurrences.

TABLE I
Incidence of Recurrent Hyperthyroidism
 (as reported by various authors)

<i>Authors</i>	<i>Number of Patients</i>	<i>Per cent of recurrences</i>
Thompson Morris and Thompson (1930)		
Various clinics		0.25 — 25%
Massachusetts General Hospital (1920-1929)	190	19.5%
Joyce (1931)		
Portland Clinic (Portland, Oregon)		5.7% (hyperplastic goiter) 3.6% (adenomatous goiter)
Buchbinder (1931)	582	3.3% (those requiring a second operation)
Gillette	108	6.5%
Cattell (1939) Cattell and Morgan (1939) Cattell and Perkin (1939)		
Lahey Clinic (1928-1937)	4,956	3.7% (those operated upon for recurrent hyperthyroidism)
Preston and Thompson (1942)		
Presbyterian Hospital (Chicago) (1930-1939)	212	17.5% (exophthalmic goiter)
	82	2.4% (toxic adenoma)
DeCourcy (1942)	1,000	less than 1%

nearly complete the thyroidectomy, the less responsive is the gland to any stimulation which may tend to cause an increase in activity. Many reports have established these general rules, which, however, have important exceptions.

It would seem that the intensity with which the causative factors in the disease continue to act may be a modifying influence affecting the relationship between the amount of remaining thyroid tissue and the degree of postoperative thyrotoxicosis. A small per cent of patients manifest definite hyperthyroidism even though little or no palpable

tissue remains (Phemiston and Delaney, 1933, Haines and Pemberton, 1936, Moorhead, 1940) Nevertheless, Preston and Thompson noted a rough parallelism between the amount of thyroid tissue palpable after operation and the degree of postoperative thyrotoxicosis, although there were significant exceptions Thus regeneration of thyroid tissue was observed in 74 per cent of patients with postoperative thyrotoxicosis whereas such regeneration was observed in only 15 per cent of patients who did not show hyperthyroidism after operation These authors have stated The presence of palpable thyroid tissue after operation is evidence in favor of thyrotoxicosis until proved otherwise Cattell and Morgan (1939) found that palpation of the thyroid gland after operation does not reveal accurately the amount of thyroid tissue remaining because the scar tissue makes it difficult to outline the lateral lobe Preston and Thompson noted that palpation is difficult for only a few weeks after operation, when induration appears and therefore in many patients thyroid tissue can then easily be palpated and can often be observed to regenerate or regress in amount Reinhardt (1942) has reported on a method of determining completeness of thyroidectomy using radioactive iodine The extension of such investigations, when radioactive iodine becomes generally available, may be expected to provide us with more definite information along these lines and should open new ways to improved therapy

Just why, in certain cases, the remaining thyroid tissue undergoes regeneration is a most important problem, this regeneration may be regarded as evidence that the cause of the disease is still active An equally important problem is that of hyperthyroidism induced when only a minimum of tissue is left at operation and no regeneration of this tissue can be observed Finally, in any discussion of the causative factors in recurrent hyperthyroidism, the possible significance of infection, overwork, pregnancy and psychic factors must at least be mentioned Although the precise roles played by such factors are still obscure nevertheless all clinicians know that one or more of these factors must be assumed in many cases to act as precipitating influences in recurrent thyrotoxicosis

Prevention As regards the avoidance of persistent and recurrent thyrotoxicosis, it is no longer a problem with us to decide how much gland should be allowed to remain when doing a thyroidectomy Our experience as well as that of many others has established that it is

better to remove too much rather than too little of the tissue. It should not be forgotten that it is far easier to control hypothyroidism than it is to overcome hyperthyroidism. The administration of desiccated thyroid will maintain a normal basic metabolic rate in cases of the former condition, but at present surgery is our only certain recourse in the latter instance. The results with thiourea, thiouracil and propylthiouracil are as yet inconclusive.

We do not, however, perform a complete thyroidectomy. We always leave sufficient thyroid tissue at the posterior portion of the gland so that subsequent scar tissue formation does not jeopardize the recurrent nerves or the parathyroid glands. As a consequence of such surgical procedure, together with our present methods of postoperative care, a normal basal metabolic rate can be maintained after thyroidectomy.

In one phase of our postoperative treatment we diverge from customary procedures and we attribute much of our success to this therapy. In our last series of 1,000 thyroidectomies, our recurrence rate has been less than 1 per cent. At the DeCourcy Clinic we have found that by administering one half grain of thyroid extract twice a day after all thyroidectomies, over a period of a year or more if necessary, we no longer need fear the recurrence of hyperthyroidism. In fact, our recurrence rate is practically nil, and this holds true even though the patient frequently returns to the same life that he or she was leading when the hyperthyroidism developed.

We have been prescribing desiccated thyroid in one half grain doses twice a day beginning about 2 weeks after the thyroidectomy, as a means of maintaining the basal metabolic rate within normal limits. Such treatment is continued for at least 3 months. After this time the patients are observed regularly at 1 month intervals and repeated metabolism tests are made. Where such examination and tests indicate that the residual portion of the gland does not maintain the basal metabolic rate within the normal range, that is, if the reading falls below minus 10, administration of desiccated thyroid is resumed. This follow up and medication are continued over a period of several years, if necessary. Obviously, the administration and dosage of desiccated thyroid must be individualized and based upon frequent observations and metabolic tests.

We feel that, by keeping sufficient thyroid in the blood stream following operation, the thyroid remains at rest, as it were, and that re

currence of hyperthyroidism will not ensue. In our opinion this is the answer to the prevention of recurrences, which have previously been reported in what must be considered a high proportion of cases.

This thyroid medication also tends to prevent sluggishness, aching and cramped muscles, puffiness of the face and other symptoms which have been of frequent occurrence after thyroidectomy. It must be pointed out that such thyroid medication constitutes only a part of the procedure, though indeed an important part. The administration of the drug must be accompanied by an orderly and healthful mode of living.

We began to use this form of treatment postoperatively several years ago, after we had discovered that desiccated thyroid extract was more beneficial in the treatment of non toxic diffuse goiter than was iodine. As a matter of fact, we have had striking results in the treatment of such goiters by the oral administration of thyroid than by depending solely upon iodine as heretofore. Non toxic diffuse goiter regularly diminishes in size and disappears following use of thyroid extract, whereas, after iodine therapy, the thyroid gland frequently becomes bosselated and enters into the phase of nodular goiter.

On the basis of our experience and theory that the administration of thyroid extract causes an atrophy of the gland due to disuse, we have used this treatment upon a number of patients with diffuse toxic goiter who refused operation. The following is one of the case reports.

Mrs. H., age 35, was examined at the Clinic on March 5, 1941, and was found to have exophthalmic goiter with marked protrusion of the eyeballs. Her basal metabolic rate (3 readings) was plus 65. The pulse rate was 130. She had lost 15 pounds in weight during the preceding 2 months. She was advised to have a thyroidectomy but refused operation.

On March 12, she was given Lugol's solution, 10 drops 3 times a day. This medication was continued until March 27, at which time the maximum effects of the medication seemed to have been attained. Her basal metabolic rate had dropped to plus 39. The dosage of the Lugol's solution was then reduced to 5 drops once daily and 1 grain of desiccated thyroid was given twice daily.

On April 10 the administration of Lugol's solution was stopped and 1 grain of desiccated thyroid twice daily was continued. On this date the patient had shown a weight rise from 118 to 130 pounds, a gain of 12 pounds in 5 weeks. Her thyroid had undergone involution and her systemic condition was greatly improved. Her pulse, after rest, was 86.

Examination on June 6, 2 months later, during which time 1 grain of thyroid extract twice a day was taken exclusively and continuously, showed a distinct improvement. Although her basal metabolic rate still remained plus 35, the size of her thyroid had diminished to one half of what it had been two months previously. Her weight had increased by 2½ pounds to a level of 132½ pounds. Tremor had diminished, but her heart beat, with a rate of 86, was still high. Thyroid, 1 grain twice daily, was continued.

On June 20, the patient's weight had increased to 137 pounds. The basal metabolic rate was plus 33. Tremor was markedly lessened, the thyroid had diminished in size and was of colloid consistency.

On August 15, the patient's weight was 134 pounds, basal metabolic rate was plus 13, tremor was absent, the heart rate was 78 sitting, and 72 resting in bed. The thyroid was still palpable but had continued to diminish in size.

The work of Rienhoff (1940, 1941) has provided impressive evidence in favor of our views along these lines and has done much to elucidate the physiological bases for such therapy. In 1940 Rienhoff reported that, from the clinical as well as the histological standpoint atrophy of the thyroid gland could be produced in cases of simple diffuse goiter and nodular colloid goiter, as the result of the oral administration of desiccated thyroid.

The changes observed in the histological structure of the thyroid appear to substantiate his hypothesis that the secretion of the thyroid in the blood stream probably determines the degree of activity of the thyroid parenchyma at any given time. Thus, in his opinion, the cellular activity of the gland would proceed at a minimum rate in the presence of an abundance of exogenic thyroid principle in the blood stream.

In his later paper (1941), Rienhoff remarked: "Tentatively it may be suggested that the administration of desiccated thyroid to patients with hyperthyroidism brings about, in some cases at least, a functional atrophy of the thyroid gland." In at least one of his more recent series of cases, there is evidence which indicates that thyroid medication resulted in structural atrophy of the thyroid gland.

While at this time we would not recommend exclusively medical treatment of exophthalmic goiter, we feel that our experience should dispel the older concept that giving thyroid extract to these patients is only "adding fuel to the fire." We realize that this treatment is not new, having been used to a limited extent many years ago, but in the meantime our understanding and methods of differentiation of thyroid

diseases have vastly improved so that now we are able to try this treatment where true hyperthyroidism actually exists

Our experience with this type of medical treatment of exophthalmic goiter is quite limited and may not be extended so as to permit general application. Nevertheless, our results with postoperative thyroid medication in thyrotoxicosis show that thyroid therapy serves as a preventive of recurrences and adds greatly to the comfort of patients who have undergone thyroidectomy. We also feel that we have dispelled the fear of using desiccated thyroid postoperatively in these cases.

In common with a number of other workers we believe that, whereas involution of the gland occurs as a result of the preoperative use of iodine, its value is only temporary; the continued use of iodine will not prevent the return of the hyperthyroidism. Because of this fact we have always considered it useless to give iodine postoperatively over a long period of time. The portion of the gland which is allowed to remain at operation remains hyperplastic, so that thyroidectomy is only a quantitative approach to a cure rather than a qualitative one. Consequently, if one can cause a disuse atrophy to occur in the remaining portion of the gland by giving thyroid extract, we shall have gone a long way toward the permanent relief of hyperthyroidism.

Treatment. In a certain percentage of cases, recurrent hyperthyroidism responds, at least temporarily and to a limited extent, to administration of iodine, but, in general, the results are unsatisfactory, according to most authorities. The use of desiccated thyroid would seem to be indicated, with a view toward the development of an atrophy resulting from disuse, as explained in the preceding section. A number of clinicians have employed roentgenotherapy with some degree of success. Further investigations may show that propylthiouracil or some other thio drug can be used to bring about the desired remission.

In the event that medical measures or roentgen therapy do not serve to keep the basal metabolic rate within or near the normal range, and especially if the symptoms of thyrotoxicosis become increasingly severe, a second thyroidectomy may become necessary. Two facts would seem to be of the utmost importance in this connection: (1) The course of postoperative thyrotoxicosis resembles that of the untreated disease, and (2) the technical difficulties involved in a second thyroidectomy may be very great. With regard to the first

consideration, as in the case of the untreated disease an exacerbation of symptoms may be only temporary and it may be advantageous to wait for a subsidence of symptoms, in the meantime, medical measures may begin to have their desired effect. One must be very sure that an operation is actually indicated, and this assurance can only be gained after prolonged and careful study of the individual case.

Dinsmore and Crile (1941) have stressed the problems of a second thyroidectomy. In secondary operations, the morbidity is greatly increased, and the incidence of technical accidents is almost 4 times as high as in primary thyroidectomies. These authors have stated: "There is perhaps no operation which can be so difficult as the adequate removal of a brittle, hyperplastic and vascular recurrent goiter." The inflammatory reaction following the first operation may have drawn the recurrent nerve into the capsule of the gland, and the jugular vein may have become adherent to the lateral border of the gland. The scar tissue often conceals the parathyroid glands, some of which may have, however, been removed at the first operation, the location of the remaining parathyroids may be expected to be atypical. Hence such an operation requires maximum surgical skill as well as the greatest possible care of the patient—preoperatively, during the operation, and postoperatively. Dinsmore and Crile have found that the percentage of second recurrences of thyrotoxicosis (i.e., recurrences after a second thyroidectomy) is approximately that of primary recurrences. In view of these facts, it would seem all the more important that adequate precautions be taken at the time of the first operation so that persistence or recurrence of the disease may not eventuate.

EXOPHTHALMOS

Increased Prominence of the Eyes Following Medical and Surgical Treatment. Soley (1942, 1944) has shown that, following thyroidectomy for exophthalmic goiter, the prominence of the eyes frequently increases even though improvement in the exophthalmos is suggested by the patient's gross appearance (because of diminished retraction of the lid and lessened contraction of facial muscles). This observation has been confirmed and extended by Dobyns (1945) and Dobyns and Haines (1946), of the Mayo Clinic. In fact, Dobyns and Haines, making actual measurements of the position of the eyes by means of the Hertel exophthalmometer, have established that, *usually*

in cases of exophthalmic goiter some protrusion of the eyes is produced not only by thyroidectomy but also by the administration of either iodine or thiouracil before thyroidectomy. Further, development of myxedema is accompanied by an increased prominence of the eyes. In most cases, the increase is of slight magnitude. Administration of desiccated thyroid was followed by a slight decrease in the prominence of the eyes of myxedematous patients. Because of the rapidity with which the increased protrusion decreased during treatment of myxedema Dobyns and Haines suggested that an increase in the amount of fluid in the tissues of the orbit may be at least one factor in the production of the protrusion.

In this connection it is noteworthy that very severe exophthalmos has been reported by other authors to be a rare manifestation resulting from some toxic effect of thiouracil (Williams and Bissell, 1943, Barr and Shorr, 1945). This observation and the findings of Soley and of Dobyns and Haines focus attention on the possibility that the orbital changes occurring in severe progressive exophthalmos may be similar to those of minor degree following thyroidectomy or administration of iodine or thiouracil. On this point, Dobyns and Haines have remarked:

It is possible that the slight global protrusion which so often follows thyroidectomy, administration of thiouracil, or the development of myxedema may be an added factor of some significance in those cases in which other factors predisposing to severe, progressive exophthalmos are present. These authors found some evidence that thyroid stimulating hormone is not responsible for the protrusion in these cases.

In the series of Dobyns and Haines, all cases treated with thiouracil showed some increase in the prominence of the eyes. The increase varied from 0.5 mm. to 4.75 mm. In the majority of cases, the increase was 1.5 mm. or more. In one case, the eye changes were alarming. As the basal metabolic rate fell from +33 per cent to -5, the prominence of the globes increased from 20.5 mm. to 25.25. Edema increased, chemosis developed, and there was pain in and behind the eyes. Even after the administration of desiccated thyroid and, later, iodine the eye signs and symptoms continued to increase. After cessation of the administration of thiouracil, medication with iodine and desiccated thyroid being continued, the appearance of the eyes improved and the pain disappeared.

Marked Exophthalmos and Progressive Exophthalmos Following

Thyroidectomy In patients with marked exophthalmos before operation, usually only minor improvement in the gross appearance of the eyes may be expected after thyroidectomy, and, therefore, no promises as to the amount of recession should be made to the patient before operation. Generally, the extent of the improvement depends largely upon the duration of the condition before operation. In advanced cases, there may be (1) slight recession, (2) no recession, or (3) slight, or, more rarely, serious progression of the exophthalmos. At times, as a sequel to thyroidectomy, marked exophthalmos may appear for the first time.

Exophthalmos may develop in association with acute hypometabolism, and the eye changes may suggest persistent or recurrent hyperthyroidism. Clearly, a second thyroidectomy might then result in serious damage to the eyes. Whenever recurrent hyperthyroidism is suggested by eye signs and symptoms, the eyes should be observed carefully and the patient should be studied painstakingly to determine the precise condition, the exophthalmos of acute hypometabolism with rapid edema may stimulate the exophthalmos of hyperthyroidism.

Many cases of malignant or progressive exophthalmos develop postoperatively even though no exophthalmos existed prior to thyroidectomy. As Ruedemann (1941) has pointed out, malignant exophthalmos is frequently associated with few other evidences of thyroid disease, this fact strongly suggests that hyperthyroidism *per se* does not explain the clinical picture. The basal metabolic rate may not be as high as might be expected, the pulse rate may not be very high and the weight loss may not be great. The occasional patient may actually gain in weight. In both the upper and the lower lids, the edema is similar to that seen in severe myxedema. These patients have venous engorgement and may have papilledema. Often they are wracked by headaches.

The exophthalmos may be slowly or rapidly progressive, or it may show periods of quiescence when no detectable changes occur. Over a period of months or years, in some patients there may be a slight improvement or at least a cessation of progression (Means, 1945). If through some unfortunate error in judgment these patients are considered to have recurrent hyperthyroidism, and a second thyroidectomy is performed, not only may the general health be impaired but anterior luxation or even death may result.

The number of cases of malignant exophthalmos may be reduced by careful study and proper selection of patients before operation. Means (1914) has stressed that thyroidectomy must be avoided in cases in which the development of hyperophthalmopathic Graves disease may seem likely. As regards exophthalmos which does appear post-operatively, certainly all will agree with Ruedemann. 'Scrupulous care exercised at the time of onset of the exophthalmos to prevent additional operations upon the thyroid gland and adequate treatment with large doses of thyroid extract will reduce still further the incidence of this type of proptosis.

The majority of clinicians agree that in many cases when exophthalmos is treated early by administration of adequate amounts of desiccated thyroid it may halt the disease, some patients may show a slow improvement. It is advisable to give thyroid extract to the point of tolerance, the dosage being regulated in accordance with the signs and symptoms and repeated determinations of basal metabolic rate. These patients generally have a high tolerance for desiccated thyroid. The most careful consideration and attention must be given to all cases of malignant exophthalmos, one of the most serious of medical and surgical problems. It is to be remembered that an exophthalmos may be apparently stationary for many months only to become suddenly *progressive and definitely malignant*, so that corneal ulceration and loss of the eye may result.

When exophthalmos has reached an advanced phase the eyes must be protected with great care. The chief danger is drying of the cornea with resultant exposure keratitis (Means, 1945), ulceration and perforation may follow. As symptomatic treatment, plain vaseline may be used to grease the lids, goggles may be necessary to protect against dust. Some authorities recommend that the lids be kept closed with tape or bandages. When the eye is in danger, tarsorrhaphy and enucleation may eventually become necessary (Poppen, 1944). For the emergency relief of this condition, decapping of the orbit according to the method of Naffziger (1931) would seem to be the procedure of choice. Such radical surgery should be used only as a last resort (Poppen, 1944, Means, 1945). Means has emphasized that most of these cases may be treated conservatively and expectantly, provided they are regularly and carefully examined, in many instances there may be a halt in the progress of the disease.

Causative Factors in Malignant Exophthalmos There is considerable evidence favoring the view that thyrotropic hormone of the anterior pituitary is the chief factor in the etiology of malignant exophthalmos. The most recent reviews of the literature are those of Brain (1945) and Means (1945). Additional evidence has been set forth by Dobyns (1946) in a series of studies on the exophthalmos producing effect of a variety of preparations of thyrotoxic hormone. Dobyns has shown that, in guinea pigs, Antuitrin T produces toxic manifestations: weight loss and exophthalmos. A purified thyrotropic preparation causes hyperplasia of the thyroid epithelium of intact animals but does not produce exophthalmos or toxic effects in thyroidectomized animals, whereas a crude thyrotropic product produces exophthalmos and slight toxic manifestations in thyroidectomized animals as well as hyperplasia of the thyroid epithelium of intact animals. These investigations and Brain's researches, which have served to focus attention on the relationship of fat metabolism to exophthalmos (Brain 1945), may be expected to lead to further, important advances in this field. New findings which will have practical application are sorely needed for, as Ruedemann (1941) has well said, toxic goiter and malignant exophthalmos present some of the most serious problems related to diseases of the endocrine system.

DISTURBANCES OF OCULAR MUSCLES

Ocular muscle disturbances are of frequent occurrence in thyrotoxicosis; they are the most persistent of all the eye signs in thyroid disease (Ruedemann, 1941). The patient may experience much trouble and discomfort from the muscle error long after all other signs and symptoms of this disease have disappeared. Ruedemann has pointed out that isolated muscle paralysis is common and bilateral muscle involvement may occur; the muscles most frequently affected are the right superior rectus and right external rectus. Because of the slowness of recovery from the thyrotoxicosis, no operation on the ocular muscles should be considered sooner than 6 months to 1 year after thyroidectomy.

IMPORTANCE OF PERIODIC EXAMINATIONS

Every patient who has undergone a thyroidectomy should be examined at regular intervals postoperatively, so that possible late complications may be detected and treated early. At each examination, the following determinations should be made: basal metabolic rate, electrocardiogram, hemoglobin. The basal metabolic rate determination will, of course, provide important information as to the progress of the patient and may serve to indicate the onset of either hypothyroidism or recurrent hyperthyroidism. The electrocardiogram is essential in cardiac cases, it must of course be remembered that in these patients there will be either a potential or an actual cardiac condition for the remainder of their lives, and they must be followed and treated accordingly. Anemia is not seldom associated with the hypothyroid state, but it does occur also in hyperthyroidism (Boenheim et al., 1945). Furthermore, at the time of the periodic visit, the patient's general condition should be observed carefully, for any signs or symptoms of hypo- or hyperthyroidism. Because of the possible late development of exophthalmos the eyes also should be carefully examined, as has already been mentioned, exophthalmos may develop either in the hypothyroid or the hyperthyroid condition, or may even become malignant in the absence of any other symptoms or signs attributable to thyroid disease.

Optimal results in thyroid surgery are attainable only when each patient is studied as an individual, is followed carefully through the months and years, and is promptly and adequately treated should any late complication eventuate.

REHABILITATION

Patients who have had thyrotoxicosis require careful supervision and sympathetic understanding on the part of the physician if they are to lead a normal life, free from recurrence of their former condition (DeCourcy, 1941). Of vital importance is adequate physical and mental rest. The patient must learn to relax and should engage in pleasurable activities, in moderation. Fatigue and such mental stresses as worry, excitement and similar psychic disturbances are to be avoided. Although few authorities would go so far as Pemberton (1930), who expressed the belief that psychic factors are the chief causes of recurrent hyperthyroidism, nevertheless probably most clinicians would

agree that such factors may often precipitate a recurrence of hyperthyroidism when the basic cause is still present, either latent or active in some degree (Berlin and Gargill, 1940, Preston and Thompson, 1942) A good diet also is essential to the optimal wellbeing of the patient who has undergone thyroidectomy, and he or she should be so informed

Of course, it is quite inadvisable that the thyroid patient come to regard himself as a chronic invalid The patient should, rather, be tactfully led to the realization of the significance of a wise mode of daily existence in the prevention of the recurrence of the former state of invalidism

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CHAPTER XVI

FUTURE OF THYROID SURGERY

CERTAIN statements concerning the future of thyroid surgery would appear to be universally acceptable. Progress will continue, surely along many different lines. Hence we can confidently look forward to an extension of certain gratifyingly successful trends not only in the actual practice of thyroid surgery but also in basic research upon which every advance, of course, depends.

During recent years, the mortality rate following thyroidectomy has been reduced so that now, in the clinics where large numbers of operations are performed, it averages between 0.5 and 1.5 per cent. Analysis of the factors which have made possible this reduction would seem to point to its continuation. Methods of diagnosis and of estimating operability and degree of thyrotoxicosis have been improved, the patient has been given the advantages of better preoperative and postoperative care as well as of refinements in surgical technique.

A greater understanding of the diagnostic significance of the typical signs and symptoms and their variability in hyperthyroidism now permits earlier as well as surer diagnosis and therefore earlier treatment. The physician and the surgeon more readily recognize cases of apathetic or masked hyperthyroidism. With reason, we may expect that methods of determining serum iodine level and concentration of circulating hormone will be rendered still more sensitive and accurate, such measurements are guides to treatment as well as to diagnosis. Still other tests, as yet in the earliest stages of development, should enable us to determine with greater precision than at present the condition of the thyrocardiac patient, the optimal time for operation, and the probability of circulatory failure during or after operation.

The geriatric patient has presented special problems, not only as a potential thyrocardiac but also as a patient whose reactions to drugs, common procedures, and surgery are to a large extent unpredictable. Also, the elderly patient usually has complicating disorders along with hyperthyroidism, his vital reserves have been drained by the years and

by diseases of long duration, and his psychic manifestations and reactions are markedly different from those of the younger patient. It is, of course, these poor risk cases — the elderly, the thyrocardiac, the diabetic, and others with complicating disorders — which show the highest mortality rate. The future should witness the devising of much better methods of management of such cases. Geriatrics may be said to be only in its infancy, but its contributions have already been immensely helpful in extending the knowledge of the special procedures which give the best results in the medical and surgical treatment of thyroid disease as encountered in the aged. The special management indicated for patients in all age groups who have complicating disorders of a chronic or degenerative nature is gradually being worked out so that results are increasingly satisfactory. This trend should continue, researches upon degenerative diseases are being planned and pursued to a far greater extent than in the past.

The outstanding factor in the reduction of the mortality rate in thyroid surgery has been the use of iodine in the preparation of the thyrotoxic patient for thyroidectomy. And just as Plummer pointed out convincingly the value of iodine in preoperative medication of the patient with Graves' disease and so instigated a major advance, so Astwood recently demonstrated clinically the beneficial effects of thiouracil, and thus marked the opening of another new era in the therapy of hyperthyroidism. At first, as some claimed, it seemed possible if not probable that thiouracil, thiourea or perhaps some more effective less toxic goitrogenic agent would be employed to the exclusion of iodine in preoperative medication. These goitrogenic agents appear to have an already established place, and a very important one, in the treatment of hyperthyroidism. As we have mentioned in another chapter (page 156), goitrogenic agents do have numerous toxic side effects and have caused a small percentage of fatalities but, unless these drugs are eventually shown to be insidiously and profoundly toxic in some way or ways still unknown, their use will be extended at least in the preoperative treatment of certain types of patients. Goitrogens would appear to be most valuable in the preoperative medication of the following types of patients: (1) Patients with Graves' disease who are not benefited by iodine medication, about 3 per cent of cases of exophthalmic goiter not responding to this medication, (2) Patients having an idiosyncrasy to iodine, (3) Patients rendered iodine fast by ill

advised prolonged treatment with iodine, and (4) Extraordinarily thyrotoxic patients

As the present low mortality proves, the average patient with Graves disease can be brought to operation with an adequate margin of safety by proper preoperative medication with iodine. Unless there are errors in management of the case or errors on the operating table, the fatalities that do occur are almost invariably among the poor risk patients. Decisive statistics concerning the advantages to be derived from thiouracilization rather than iodination of the poor risk patient have not yet been forthcoming, however, thiouracil as a rule does effect a greater decrease in toxicity than does iodine. Thiouracil or another goitrogen may be indicated — by the results of present and future investigations — in the preoperative medication of patients who are fair risks or poor risks.

Proper iodination of the patient is still necessary, and in all probability will continue to be necessary, in preoperative medication whether or not a goitrogen is also employed. Thiouracilization without a course of iodination causes technical difficulties at operation: the thyroid gland is more friable and hemostasis is less readily achieved than when the patient has been properly iodinated.

Many authorities have warned of the possible danger of carcinogenesis by goitrogens when employed in the treatment of patients with toxic nodular goiter. The trend of present investigations is toward the confirmation of such misgivings and if such confirmation is clear and indubitable, then other considerations come to mind. A certain percentage of individuals in every age group, and perhaps 40 to 50 per cent of the elderly (as shown by routine postmortem examinations of all types of fatally terminating cases) have been shown to have nodules in the thyroid. Most of these nodules are of the colloid adenomatous type, and probably represent local areas of hyperinvolution with fibrous capsules, the danger of eventual malignancy is believed to be low. But discrete adenomas although occurring less frequently than colloid adenomatous nodules, are far more likely to undergo malignant degeneration. Just what effect, if any, prolonged administration of goitrogens will have upon such nodules in hyperthyroid patients of all types cannot be determined for many years. It may or may not be advisable to use thiouracil therapy as the sole treatment of hyperthyroidism, such medication must be prolonged over many months. Many cures follow

ing this form of therapy have been reported, and the reported rate of temporary remissions is much higher. Still, the conservative consensus is that the best treatment of toxic goiter is early thyroidectomy — performed as soon as the operability has been rendered satisfactory by preoperative medication, whether by iodine or by iodine and a goitrogen.

Prolonged thiouracilization — over a period sufficient to permit some temporary remission or perhaps an apparent cure — is costly, and in many cases would be more costly and more inconvenient to patient and physician than thyroidectomy. Recurrence after thiouracil therapy as the sole treatment is frequent. Another course of medication, if not thyroidectomy, is indicated in every recurrence; the cost is then increased. And every course of thiouracil medication necessitates frequent examination of the patient to determine whether or not toxic reactions are developing.

In many localities, clinics with the personnel and facilities for satisfactory treatment of the thyroid patient have not yet been established. And it is in these areas that medical management of exophthalmic goiter by thiouracilization may be found to give better results than thyroidectomy performed under adverse conditions. The risks of course may be great, but in such localities the mortality rates before, during and after thyroidectomy are much higher than the rates reported from leading clinics. Besides many patients go untreated altogether. One consideration above all others seems worthy of special emphasis. Will encouraging reports of results of goitrogen therapy in exophthalmic goiter tempt the inexperienced to undertake the medical treatment of all cases of toxic goiter — and cases of apparent hyperthyroidism? Differential diagnosis remains a difficult problem.

The results of the surgical treatment of cancer of the thyroid have improved in recent years but the advances in this field are scarcely comparable to those in the therapy of goiter. Even the comparison of results of earlier therapy and more recent methods of treatment of thyroid cancer is difficult — as is comparison of results from different clinics today. To achieve a clear cut evaluation of clinical results in the treatment of cancer of the thyroid gland we must have more satisfactory methods of classification of thyroid tumors. Some regard practically all papillary tumors as benign, other authors classify these tumors as benign or malignant in accordance with the generally accepted criteria of malignancy. Nomenclature differs according to the authority. Recorded re

sults often do not indicate the extent of pathology encountered at operation. These sources of confusion naturally retard the development of a better understanding of thyroid cancer, its treatment and the prognosis when a particular type of tumor is encountered in the clinic. What progress has been made along these lines cannot be called satisfactory. Optimism is inspired, however, by the increasing realization of the need for uniform methods of classification and of reporting results in terms of extent of involvement.

Because of the possibility of the development of pressure manifestations, thyrotoxicosis and cancer in cases of non-toxic nodular goiter, there is a decided trend toward the prompt removal of such tumors. When the nodule is solitary and the patient young, the probability of the ultimate development of carcinoma is now generally believed to be high enough to establish the necessity for the excision of the growth. It seems likely that the number of such prophylactic operations will increase.

Much difference of opinion still exists as to the origin of lateral aberrant thyroids. A number of authorities regard it as already established that these tumors take rise from small neoplasms within the thyroid gland proper. If this view prevails, then the treatment of lateral aberrant thyroid masses must include not only their excision but also exploration for the primary tumor and its removal. This type of thyroid tumor is extremely radiosensitive and therefore operation for removal of the tumor masses is now commonly followed by intense irradiation therapy.

Radioactive iodine has been used in the treatment of cancer of the thyroid, and some of the early reports are encouraging. In a number of patients, some benefit, however evanescent, has resulted from therapy with this new agent. It is far too early to attempt to evaluate this form of treatment. Several different isotopes, all radioactive, are becoming available in increasing quantities. The long range effects of none of them have been investigated. Each isotope affords a new method or system of methods of attack, differing according to the isotope with its own particular half life and intensity of effect. Varying mixtures of different isotopes may offer possibilities still unsuspected.

The value of radioactive iodine in localizing functional metastases from cancer of the thyroid gland has already been demonstrated. More accurate determination of prognosis in at least certain cases of thyroid

cancer should eventually be made possible. Results obtained thus far with other isotopes (radioactive phosphorus, for instance) in the attempted diagnosis of cancer wherever situated have met with some success, in a high percentage of cases, findings with the radioactive isotope technique corresponded with the clinical and pathologic findings. Radioactive iodine, therefore, is not the sole available radioactive material which may at some future time permit early diagnosis of thyroid cancer. Indeed, it is not the only radioactive substance which may have value in the treatment of neoplasms of the thyroid gland. Radioactive isotopes of bromine, another member of the halogen family, may be found to have valuable therapeutic effects.

Of all the studies with radioactive iodine those in which the new isotopes have been used as tracers have proved the most profitable up to this time. Basic knowledge concerning the metabolism of iodine and the nature of the thyroid functioning in health and disease from prenatal life to advanced age has been gained (page 177). These investigations are being extended to every conceivable phase of thyroid activity, and we must expect revolutionary changes in present theories as to thyroid physiology and pathology, radioactive isotopes are more sensitive and much easier to use as indicators than deuterium and the heavier isotopes of carbon and nitrogen whose introduction into research was speedily followed by radical alterations in our conceptions of the metabolic roles of fatty acids and amino acids. Other basic research is giving us new information concerning the chemical nature and physiological action of numerous different types of iodine-containing proteins, including both synthetic and naturally occurring molecules. These studies should aid in the solution of the great problem. Does the thyroid gland of the thyrotoxic individual actually elaborate some definitely toxic substance — cytotoxic, cardiotoxic, or abnormally stimulating to special tissues, such as those of the liver, the adrenals, other endocrine glands, or the nervous system? The discovery of one or more toxic products (iodine containing or not) from the diseased thyroid gland would presumably be followed by the development of qualitative and quantitative tests to promote the further improvement of diagnosis and therapy. Even negative findings would be helpful. More importance would have to be attached to other possible factors in the causation of (1) exophthalmic goiter, (2) toxic nodular goiter, and (3) thyroid crisis.

It is both pertinent and interesting to note that, although the most serious phases of toxic goiter and its surgical treatment have been dealt with very successfully, nevertheless the basic causative factors in affections of the thyroid remain undetermined. It has not yet been established that the underlying pathology of exophthalmic goiter and toxic adenoma is one and the same, as many investigators believe. Indeed, the characteristically different response to iodine medication (pre-operatively) in the two conditions is strong evidence against this hypothesis. Another great problem is that of the variation among individuals in their response to thyrotoxicosis. These are fascinating theoretical considerations but they are fundamentally practical also. As soon as the basic researches now under way increase our understanding of thyroid pathology and physiology, practical applications will be devised. Such confidence is fully justified, as the history of medical science has demonstrated a myriad fold in its progress through the ages.

INDEX

A

Abel, M.S., 88
Abelin, 20, 22
 Aberrant (ectopic) thyroid tissue, 35-36, 40, 372
 aorta, 35
 fetal adenomas, 35
 fetal parenchyma, 35
 foramen cecum, 35
 glandular cell masses, 35
Grüber, 35
 in the mediastinum, 35
 non differential masses or fetal follicles, 35
Porta, 35
 thyroglossal tract, 35
 tumors, 35
von Haller, 35
 within thoracic cavity, 36
 Aberrant thyroids, 26, 29, 36-39
 intraesophageal thyroid, 37
 intralaryngeal thyroid, 37
 intralingual thyroid, 36
 intrathoracic goiter, 37
 lateral aberrant thyroids, 36
 lingual thyroid, 36
 location of, 36
 nasopharyngeal thyroid, 37
 osseous system, 38
 prelaryngeal thyroid, 37
 retrolaryngeal thyroids, 37
 retrotracheal thyroid, 37
 struma ovarii, 37
 sublingual thyroid, 37
 submaxillary triangle, 37
 supraclavicular fossae, 37
 within the pericardium, 37
 within the pleura, 37
 Abnormal heart sounds, 323
 Absence of one lobe, 38
 Absence of the isthmus, 38
 Absence of the thyroid gland, 38
Aschoff, 38

Wells, 38

Absorption, distribution and elimination, 151-152
 absorption of thiourea, cystine cysteine, thiocyanate, thiosulfate, urochrome or melania and uracil 152
 adrenals, 152
 ascitic fluid 151
 bone marrow, 152
 cerebrospinal fluid 151
 edema fluid, 151
 pericardial fluid 151
 pituitary 152
 pleural fluid 151
 thyroid, 152
 Abundance of lymphocytes 265
 Accessory thyroid glands 66
 2 acetaminofluorine, 159
 Acidophilic colloid, 81
 Acini, 77-78, 224
 after puberty, 77
Andreu and Andreu 77
 during early childhood, 77
 effect of health, nutrition, medication, age and geographic locality 77
 in early adult life, 77
Hellwig, 78
 in goitrous regions, 78
 in infancy, 77
 in later years, 77
 in non goitrous regions, 78
 of the newborn, 78
 in senile persons, 77
Rice, 78
Rice and Hertzler 77
 sparse, 224
 Acinar degeneration, 246
 Acinar epithelium, 78-81, 252
 actual measurement of height, 80
 columnar cells 79
 effects of cold, 31

- effects of thiouracil and related substances, 80
 effects of thyrotropic hormone, 80
 endothelial cells, 79
 epithelial cells, 78
 in adult life, 79
 hypophyseal activity, 79
 in exophthalmic goiter, 80
 in infancy, 79
 in youth, 79
Langendorff, 80
 network of chromatin, 80
 normal epithelium, 79
 normal rats, 81
 papillary folding, 80
Paschke, 81
 proliferation, 80
Ranson and Starr, 80
 reabsorption of colloid, 80
 senile state, 80
Turner and Turner, 81, 91
 Acromegaly, 110, 303
 Action of iodine in thyrotoxicosis, 124
 Actions on growth and development, 95
 Acute nonexophthalmic goiter, 205
 Acute nonsuppurative thyroiditis, 242
 245-247, 261
 acinar degeneration, 246
 bacterial origin, 246
 bacteriologic and morphologic studies, 246
 edema, 246
 erroneous diagnosis of toxic goiter, 246
 fibrosis, 246
 parenchyma, 246
 pathological examination, 246
 polynuclear infiltration, 246
 symptomatology, 245
 Acute suppurative thyroiditis, 242-245
 chemotherapy, 244
 colon bacillus, 243
 exfoliated acinar epithelium, 245
 extensive military tuberculosis, 243
Hertler, 244
 hypertrophy and hyperplasia of follicular epithelium, 245
 Kocher, 243
 leukocytes, 245
 Meeker, 243
 myxedema, 244
 oxygen tent, 243
 pneumonia, 243
 polynuclear cells, 245
 pyogenic infections, 243
 staphylococci, 243
 streptococci, 243
 subcutaneous edema, 244
 surgical drainage, 244
 symptom, 241
 systemic reaction, 244
 tuberculosis, 243
 typhoid fever, 243
 Womack, 244
 Acute thyroiditis, 158
 Acute toxic goiter, 203, 206
Adams, R. C., 333, 334, 339
 Addisonian crisis, 101-102, 109
 Adenocarcinoma of thyroid, 59, 60
 219, 226-229
 carcinoma of thyroid with tendency to squamous metamorphosis, 227
 compact type, 228
 diffuse adenocarcinoma, 227, 228
 epidermoid carcinoma, 229
 Graham, 226
 not originating in adenoma, 226
 Pemberton, 228
 Pemberton and Lovelace, 227-228, 236
 Portmann, 226-227
 scirrhous carcinoma, 228
 small, round cell carcinoma, 227-228
 spindle cell carcinoma, 227-228
Adenoma malignum, 183-184
 Adenomas, 43, 158
 Adenomatous glands, 281
 Adenomatous goiter, 43, 207-210
 benign adenoma, 208
 columnar epithelium, 210
 embryonal, 208
 fetal acini, 210
 fetal rests, 208
 follicular type of fetal adenoma, 208
 histological variations, 208

- hypertrophic parenchymatous thyroid, 210
 intermediate or colloid adenoma, 208
 morphological characteristics, 207
 papillary like infolding, 210
 simple fetal, 208
 trabeculae of epithelium, 208
 Adenomatous goiters in old age, 293
 Adequate medication, 300
 Adequate rest, 300
 Administration of barbiturate, 296
 Administration of desiccated thyroid, 405
 Administration of iodine, 408
 in iodine fast cases, 296
 in nodular goiter, 262
 Adrenal cortex insufficiency, 101, 268
 Adrenal failure, 102
 Age incidence, 217
 Agranulocytosis, 156, 157
Algire, G. H., 88, 92, 116
Allara, E., 88, 287, 297
 Alphine bronchocele, 15
Althausen, 98
 Altmann Gersh freezing drying technique, 83
 Alveolar adenocarcinomas, 234
 Alveoli, 201
 American contributions, 14
 Amino acids injected, 278
 Amount of gland to remove, 355-358
 incision closed, 357
 longitudinal incision sutured, 357
 Lugol's solution, 356
 Pool and Garlock, 356, 358
 primary resections, 358
 recurrent hyperthyroidism, 358
 suture of sterno thyroid muscle to pretracheal fascia, 356
 Analysis of heart sounds, 323
 Analysis of radioactive material in blood, 179
 Analysis of thyroid tissue after operation, 179
 Anaplastic carcinoma, 368
 Anaplastic inversion, 224
 Anaplastic tumor, 234
 Anastomosing, vessels, 69
 Anastomotic branch, 68
 Anatomy, II, x, 3-4
 acini, 4
 capillaries, 4
 colloid, 4
 columnar cells, 4
 cuboidal cells, 4
 epithelium, 4
 follicles, 4
 lymphatics, 4
 structure, 4
 Anatomy, histology and cytology, 66-88
Anderson, E., 199
Anderson, G. W., 199
Andreu, N. V., 77, 84-86, 88, 288-289, 297
Andreu, R. H., 117
Andreu, W., 77, 84-86, 88, 138-146, 288, 297
 Anesthesia, 329-339
 carotid sinus syndrome, 338
 cyclopropane, 335
 DeCourcy Clinic, 329
 ether, 329
 ethylene and ether, 335
 intratracheal, 330-331
 in operations following thiouracil treatment, 333
 intravenous anesthesia, 336
 Joll, 330
 local, 329, 333-334
 morphine, 332
 nitrous oxide and oxygen, 329-330
 postoperative sedation, 333
 postoperative vomiting, 329
 removal of excess mucus, 338
 scopolamine, 332
 spinal anesthesia, 337
 tribromethanol in amylene hydrate (avertin), 337
 Anesthetics, toxic effect on liver, 296
 Aneurysm of the aorta, 45
 Angina pectoris, 19
Anglem, T. J., 165
Anitschkou, N., 290, 297
 Anlage, 50

- Anlagen of thyroid, 36
- Anomalies in relation to the hyoid bone, 39-40
- aberrant thyroid tissue, 40
- bifurcation, 39
- embryonic rests, 40
- hyoid, 39-40
- isthmus, 39
- lateral lobes, 39
- periosteum of the hyoid bone, 40
- primordium, 39
- second month of fetal life 40
- thyroglossal duct, 40
- thyroglossal fistula, 40
- thyroglossal tract, 39
- tumors, 40
- Anomalous embryonic development, 51
- Anoxemia of cells, 202
- Anoxia, 382, 384
- Anteriomediastinum, 45
- Anterior jugular veins, 68
- Anterior luxation, 411
- Anterior lobe extracts, 20
- Anterior mediastinal branches, 71
- Antithyroid drugs, ix, 149-152
- absorption, distribution and elimination, 151
- allylthiourea, 149
- Astwood*, 149
- brassica seeds, 149
- Chesney Clauson and Webster*, 149
- cyanides, 149
- effects on animals, 150
- effects on human beings, 151
- Foulger and Rose*, 149
- Hercus and Purjes*, 149
- Kennedy*, 149
- MacKenzie and MacKenzie*, 149
- sulfadiazine, 149
- sulfanilamides, 149
- thiocyanate, 149
- thiouracil, 149-150
- thiourea, 149-150
- thyroid tissue after thiouracil therapy, 152
- Williams*, 150-151
- Williams, Kay and Jandorf*, 151
- Antuitrin, T*, 113
- Arrel, I*, 195
- Arteria centralis retinae, 280
- Arterioles from the trachea 72
- Arteriosclerosis, 259
- Arteriovenous aneurysm, 279
- Ascending cervical artery, 72
- Aschoff*, 38
- Asphyxia, 393
- Astwood E B* 21-22, 88, 149, 159, 161 163, 169, 174, 195
- Atherosclerosis of aorta in rabbits, 290
- Athyreosis, 102
- Atrophic epithelium 207
- Atrophy of the thyroid, 17
- Atropine, 332
- Attachment of gland to larynx 69
- Aub J C* 20, 22
- Auricular fibrillation and flutter, 321, 387
- in diffuse nodular goiter, 324
- Avertin, 337
- ## B
- Balsterscher, J A*, 33, 61
- Bile, W' F* 195
- Bilker, H* 64
- Ball, R P*, 196, 198
- Barbital compounds, soluble, 395
- Birger* 93
- Birker, W' H*, 311, 327
- Barr, P D* 163, 410
- Bartelmez, G W'*, 60
- Birtels and Perkin* 20
- Bartels, L C*, 22, 155, 159, 263, 297, 337, 339
- Birtels, E L*, 312, 327
- Barton*, 15, 22
- Basal metabolic rate, 4, 8, 21
- Basal metabolic rate increase, 279
- epinephrine and asthmatic seizures, 279
- Feinblatt and Eggerth, 279
- Basal vacuolar substance, 83
- Basedow's disease, 206, 275, 278-279
- Basophilic colloid, 84, 207
- Bassett*, 132

- Baumann, E J*, 18, 22, 93, 104, 111, 116, 163, 195, 298
- Baxter, B* 146, 196
- Baylers, F*, 63
- Bayley, R H*, 383, 391, 398 399
- Beeson, H B* 61
- Beilby, G E* 39, 61
- Benedict, E M* 146, 196
- Benedict, F G* 289, 297
- Benign adenoma, 208, 220, 365
malignant degeneration, 363
- Benign granuloma, 253
- Benign lateral aberrant thyroid tumors 54
- Benign metastasis, 43
- Benign metastasizing colloid goiter, 55
Boyd, 55
colloid goiter, 55
Connheim, 55
dissociated tissue alveoli, 54
Luung 55
from embryonic rests 55
inferior maxilla, 55
Oderfeld and Steinhaus 55
perforating tumor of the skull 55
Riedel, 55
- Benign metastasizing struma 221
- Benign nodular goiter, 55
- Benign tumors, 53, 57, 215
- Bennett G A*, 90, 126, 148
- Bensley R R*, 82 83, 88
- Berlin, D D*, 39, 75, 88, 415
- Bernard, Claude*, 276
- Bernhard W G* 299
- Bettencourt, R* 18, 22
- Bielschowsky, F*, 158, 163
- Bifurcation, 71
- Bilateral thyroidectomy, 343-360
blunt dissection, 346
cutaneous nerves, 344
danger of tearing lateral vein, 346
dissection of right lobe, 351
elevation of left lobe, 353 354
elevation of right lobe, 347
fascial plane, 344
freeing of gland from overlying structures, 346
hemostats on branches of inferior artery and vein, 350
incision of right lobe, 351
incision through skin and platysma, 344
longitudinal incision of fascia, 345
principal accidents, 354
relationship of recurrent nerve to inferior thyroid vessels, 349
small bleeders, 344
stripping right lobe across trachea, 352
substernal goiters, 345
superior laryngeal nerve 348
superior pole, dissected free, 347
superior pole, ligation 348
thyroid remnants remaining after removal of both lobes, 355
traumatizing recurrent laryngeal nerve, 346
Trendelenberg position 343
reverse, 343
wiping down capsule, 347
- Biochemical investigations 169 176
acidophilic follicles, 176
allylthiourea, 170
Astwood, 169 174
in basophilic colloid, 176
carboxyl, 174
conversion of circumambient inorganic iodide, 170
cyanides, 170
De Robertis, 176
diiodotyrosine, 171
formation of radiothyroxin, 170
Franklin and Charkoff 169 170
Franklin Charkoff, and Lerner 170
Harrington, 171
Hertz 175
Horton 175
Keating 174
Larson, 171, 174
Leblond, 175
Leblond, Fertman, Puppel, and Curtis, 172 173
Leblond and S  e, 173
MacKenzie, 169

- Metabolism of radio iodine as affected by high and low temperatures, 177
- Morton* 176
- p aminobenzoic acid, 170
- p aminophenylacetic acid, 170
- phenylthiourea, 170
- radioactive iodine, 176
- radiodiodotyrosine, 170
- radio iodine, 175
- Ringer's solution, 170
- sulfanilamide, 170
- sulfonamides, 170
- sulfapyridine, 170
- sulfaquanidine, 170
- sulfathiazole, 170
- sulfonic acid, 171
- Taurog, Chaikoff, and Franklin* 171
- thiocyanate, 170
- thiouracil, 171
- thiourea, 170
- derivatives 170
- thyrotropic hormone, 171, 174 175
- thyroxin, 171
- tracing effects of goitrogenic substances, 170
- tracing effects of sulfonamides, 169
- utilization of radio iodine, 170
- Biological aspects, 22
- Birds, 29
- Bishop, R C* 157, 164
- Bissell A.* 88, 163
- Bissell G W* 165 110, 117
- Black, B M*, 239
- Blackman S S* 54 55, 61
- Blood cholesterol, 401
- level, 302
- Blood iodine, 132
- determination 141, 302
- Blood pressure, 318 322
- after successful operation, 319
- in brachial and femoral arteries in exophthalmic goiter, 318
- effect of thyroid secretion, 318
- essential hypertension, 319
- in exophthalmic goiter, 318
- fall after intravenous injection of crude extract of thyroid gland, 318
- fall in peripheral arterial field, 322
- fall in systolic pressure, 319
- Falts* 318
- Fishberg*, 322
- Graves disease, 319
- Handel*, 319
- hypertension, change in vascular coats, 319
- Mannaberg*, 319
- in myxedema, 321
- nephritic hypertension, 319
- Plummer* 318
- readings in myxedema, 322
- relation to basal metabolic rate, 319
- renal threshold for sugar, 320
- Taussig*, 318
- Troell*, 319
- variations, 319
- Willins and Haines* 321
- Blood supply, 69-72
- anterior mediastinal branches, 71
- arterioles from the trachea, 72
- ascending cervical artery, 72
- bifurcation, 71
- branch to scalenus anterior, 72
- bronchial arteries, 71
- Burton Ortiz*, 69
- carotid sheath, 71
- collateral circulation 72
- common carotid artery, 71
- contralateral inferior artery, 71
- cricothyroid artery 70 72
- divisions of superior thyroid artery, 70
- esophageal artery, 72
- esophagus, 71
- external carotid artery, 70 71
- glandular arteries, 70, 72
- homolateral anastomosis 71
- homolateral inferior thyroid artery, 70
- hyoid, 72
- indirect anastomosis, 71
- indirect communicating channels, 71
- inferior constrictor muscles, 72
- inferior laryngeal artery, 71-72

- inferior pole, 71
 inferior thyroid artery, 71-72
 infrahyoid artery, 70
 innominate artery, 72
 interlobular arteries, 70
 internal mammary arteries, 71 72
 intralobular arterioles, 70
 lateral anastomosis, 71
 ligation of superior artery, 70
 lingual artery, 72
 longus capitis muscle, 70
Mastin, 70 72
 omohyoid muscle, 70
 parenchymal arteries, 70
 periacinar capillaries, 70
 profuse peripheral anastomoses, 71
 ramus communicans, 70
Rienhoff, 70
 scalenus anticus, 71
 sternomastoid, 70
Steuart, 70
 subclavian artery, 71 72
 superior belly, 70
 superior laryngeal, 70
 superior lateral artery, 71
 superior pole, 70
 thyro-cervical trunk, 71
 thyrohyoid, 70
 thyroidea ima, 72
 tracheal artery, 72
 tracheal cartilages, 72
 tracheal plexus, 71
 trifurcation, 71
 vertebral arteries, 72
 volume of blood per minute, 69
Blumenthal, *H T*, 88
 Blunt dissection, 346
Boas, *E P*, 279
Bochdalek, 42
Boenheim, 414
Boothby *W M*, 100, 117, 289, 297, 339
Born, *G*, 61
Botke, *F A*, 247, 254, 271
Boyd, *E M*, 67, 88, 164
Boyd, *J D*, 63
Boyd, *W*, 55, 61
Boyd, *A M*, 262, 271
Brain, *W R*, 413, 415
Bram, *I*, 292 293, 297
 Branch to scalenus anterior, 72
Broders, *A C*, 213, 233, 238
 Bronchial arteries, 71
 Bronchocele, 15
Brown, *H P Jr*, 216 239
Bruger, *M*, 146, 284, 289 290, 297
 Bruit over thyroid, 281
Buchbinder, *W C*, 415
Bugher, *J C*, 262, 271
 Bulbous and ulcerative lesions, 311
Burton Opitz, 69
Butler, 132
Buxton, *R W*, 384, 393 394 398
Byron, *F B*, 100, 117
- ## C
- Cachexia strumipriva, 17 18
 Calcification, 241
 Calcium chloride solution, intravenous administration, 396
 Calcium deposits, 50
 Calcium lactate, 397
 Calcium metabolism, 20
 Calories per day, 306
 Calorigenic action, 94
 of thyroxin, 102
 Calorigenic potency, 105
 Cancer, 342, 366
 among patients with nodular goiter, 212
Cannon, *W B*, 19, 22
Cantarou, *A*, 90, 165
Canzanelli, *A*, 106, 117
 Capillary ooze, 385
 Capsule of Tenon, 276
 Carcinoma, 59 60, 105, 214-227, 230 342
 of homolateral thyroid lobe, 51
 in diffuse toxic goiter, 182
 in situ, 158
 of thyroid, part alveolar, part papillary, 225
 of thyroid, part diffuse, part papillary, 226

- of thyroid with tendency to squamous metamorphosis, 227
- Carcinoma sarcoma (giant cell), 220, 229
- Carcinoma simplex, 228
- Carcinosarcoma, 368
- Cardiac and elderly patients, 360
- Cardiac conditions, 307
- Cardiac hypertrophy, 323
- Cardiac weakness, 324
- Care in immediate postoperative period, 382-384
- anoxia, 382, 384
- Bayley* 383
- Buxton* 384
- dangers of oversedation, 383
- desiccated thyroid, 384
- fluids and glucose, 383
- inadequate sedation, 383
- iodine therapy, 384
- loss of fluid by vomiting or by perspiration, 383
- McIsler and Winter*, 384
- necrosis of the liver, 384
- oxygen therapy, 382
- renal function, 383
- sedation, 383
- sulfonamide therapy, 383
- thyroid crisis, 383
- Womack*, 382
- Carlson A J* 284 285, 289 297
- Carpopedal spasm, 396
- Carotid sheath, 68, 71
- Carotid sinus syndrome, 338
- hyperactive carotid sinus, 338
- Rovenstine and Cullen*, 338
- Casperson, T*, 83, 89
- Casserio Giulio* 15, 22
- Castaldi, L.* 67, 88
- Castle W B*, 99, 118
- Catabolism, 19-20
- Catalytic agent, 20
- Catheart, R T*, 164
- Cats, 19
- Castell, R B*, 52, 61, 131, 133, 137, 147, 295, 297, 405, 415
- Causation of struma fibrosa, 263
- Causative factors in malignant exophthalmos 413
- Causes of laryngeal or tracheal obstruction, 389
- Caylor H D* 90
- Cellular hyperplasia, 207-213
- Centrosome, 81
- Cerebral cortical alpha, 98
- Cervical fascia, 68 69
- Cervical or internal jugular chain 74
- Chaikoff, I L*, 126, 148 164 169 170, 174, 196, 199 200
- Chamorro A*, 198
- Changes in later life 286-289
- Allara* 287
- Andreu and Andreu*, 288 289
- Clerc*, 286
- coarsening of reticular fibrils 287
- colloide statica, 287
- compensatory hyperfunction of thyroid gland 286
- Cooper*, 286
- Dogliotti* 286-287
- epithelial proliferation, 286
- Garan* 287, 289
- general degeneration 288
- Gbigi and Reggiani* 287
- Goldzieher*, 289
- Hertzler*, 287 288
- Korenchevsky* 288
- Lansing and Wolfe* 288 289
- loss of acinar function, 288
- Nizzi Nuti* 286, 287
- presence of hyaloid connective tissue, 287
- Rice* 287
- size of follicles, 289
- studies on animals, 286
- thickening of collagenous fibrils, 289
- transformation of reticulum into collagen, 287
- Chapman E M* 187 189, 192, 195
- Charcot J M*, 22
- Charteris A A* 273
- Chatin, M A* 3, 16, 21 111, 117
- Chauffard A*, 276, 282
- Chemical composition of bone, 101

- Chemical nature of thyroid hormone, 92
- Chemical perithyroiditis, 262
- Chemotherapeutic agents, ix
- Chemotherapy of Graves' disease, 213
- Chesney, A M* 149, 164
- Chromophobic vacuoles, 82
- Chronic lymphatic thyroiditis 267
- Chronic nonspecific thyroiditis (Riedel's struma), 248-249
- Chronic thyroiditis, 242
- Chvostek's sign, 397
- Ciliated columnar epithelium, 41
- Cipra A*, 298
- Circulating sympathomimetic toxin, 275, 393
- Classical papers, 13
- Claudius Galen*, 14
- Clay, R C* 54 55, 61
- Clauson, T A*, 149, 164
- Clement, F W*, 339
- Clerc, E* 87 88, 286, 289, 297
- Clinical features, 248
- Clinical findings, 13
- Clinical practice of geriatrics, 291
- Clinical response to thiouracil therapy 153
- Clute, H M*, 63, 164 165, 215, 238, 247, 307, 312, 327, 388, 398
- Cohen, A C*, 119
- Cohen, R A*, 392, 398
- Cohn L C*, 52 53, 61, 106
- Comdet, C W* 16, 22, 111
- Cole, V V* 117, 139, 145
- Cole, W H* 210, 213 214, 238, 241, 306, 311, 317, 327, 335, 339, 398
- Collateral circulation, 72
- Collection of mucus, 387
- Coller, F A*, 262, 271, 392, 399
- Colloid, 21
- droplets, 82
- goiter, 55, 59, 201
- nodules, 87
- retention, 202
- Colloide statica, 287
- Columnar cells, 79
- Columnar epithelium, 204, 210
- Committee on Classification of the American Association for the Study of Goiter, 5
- Common carotid artery, 71
- Common duct ligation, 137
- Comparative anatomy, 29
- high vertebrates, 29
- vertebrate animals 29
- Comparative embryology, 27
- ammocoetes, 27
- amphioxus, 27
- cyclostomes, 27
- dependency of the esophagus, 27
- digestive processes, 27
- endostyle organ, 27
- nutrition, 27
- primitive chordates, 27
- thyroid hormone, 27
- tunicates, 27
- Compensatory hyperplasia 259
- Concentration of serum precipitable iodine, 313
- Congenital athyreosis 95
- Congenital cretinism 53
- Congenital hypertrophy, 38
- Congestive heart failure, 386
- Conjunctivitis, 157
- Connective tissue infiltration, 249
- Connective tissue septa, 76
- Connell W F*, 164
- Conneheim* 55
- Constitutional upset 242
- Contraction of the stylohyoid muscle 68
- Contralateral inferior artery, 71
- Contralateral inferior laryngeal artery 71
- Control of bleeding 385
- Cooper Astley* 17, 22
- thyroid in puppies, 17
- Cooper, E R*, 286, 289, 297
- Cope, A* 147, 328, 335, 337, 339
- Corpora restiformia, 19
- Cortell, R E* 200
- Courtois*, 111
- Cou gill, G R*, 306, 327
- Cretinism, 15, 17, 95, 106

Cretinoid facies, 107
 symptoms, 92
 Cretinoid syndrome, 92
Creuzberg G, 290, 299
 Cricoid cartilage, 68 69
 Cricothyroid artery, 70-72
 Cricothyroid muscles, 68
Crile G, Jr, 52 53, 61, 239, 292,
 297-298, 337, 339, 399, 409, 415
Crile, G, Sr, 239, 295, 298
Crotti, A L, 61, 247, 271
 Cuboidal epithelium, 202, 206 207
Cullen, S C, 338 339
Curling, T B, 16, 22
Curtis G M, 105, 109, 116 117, 130,
 134, 139, 145, 172 173
 Cutaneous nerves, 314, 361
 Cyclopropane, 335
Cole, 335
 contraindications, 335
Cope and Welch, 335
 effect on parasympathetic system
 335
 postoperative recovery, 335
 Cyclopropane ether, 335
 Cystic and solid ovarian tumors, 58
 Cystic degeneration, 202
 Cystic teratoma, 58
 Cystic tumors, 51
 Cysts, 48, 342
 Cytological precursors, 82
 Cytoplasm, 81

D

d Abreu A L, 60
 Damage to recurrent nerve, 262
Dandy W' E, 61
Danforth, D N, 56, 58, 62
 Danger of excess fat, 306
 Dangers of oversedation, 383
Dmowski, T S, 135-136, 115, 312-
 313, 327
Davis, C B, 117, 115
Davis, H A, 239
Davison, R. A, 117
DeBorden, T, 15, 22
DeCourcy, Carroll, x

DeCourcy, J L, 61, 121-122, 131,
 136-137, 142, 145 146, 164, 247,
 251, 269, 271-272, 304, 309-310,
 327, 339, 368, 376, 381, 402, 415-
 416
DeCourcy Clinic, vii, x, 3, 10, 15, 136,
 250, 255, 329, 405
 Degenerate nodules, 87
 Degeneration of thyroid, 291
 Degenerative changes in muscles, 101
 Degenerative type of tissue, 50
 Deglutition, 68
De Lamater, 132
Delaney P A, 404, 416
De Lee, J B, 117
Dempsey, E W', 88
 Denser eosinophilic, 84
 Depletion of hepatic glycogen, 98
De Quervain, F, 117, 217, 239, 271
 Derby neck, 15
 Dermatitis, 311
 Dermoid cysts, 56, 58
De Robertis E, 82 84, 88, 92, 117,
 176
 Desiccated thyroid, 10, 384, 398, 405,
 408, 410, 412
 Desoxycorticosterone, 102
 Determination of alcohol-insoluble io-
 dine of blood, 131
 Determination of serum iodine levels,
 132
 Detoxifying function in hyperthyroid-
 ism, 139
 Deviation of trachea, 45
 Dextrose tolerance, 98
 Diabetes mellitus, 98, 304, 307
 Diagnosis of thyrotoxicosis in aged,
 294
 Diarrhea, 19
 Diet, postoperative, 296
 Diethyl thiobarbituric acid, 159
 Differential diagnosis, 250, 303-304
 acromegaly, 303
DeCourcy, 304
 diabetes mellitus, 304
 essential hypertension, 303
 lymphatic or myelogenous leukemia,
 303

- neurocirculatory asthenia, 303 304
 pulmonary tuberculosis, 303
 therapeutic test, 303 304
Thompson, 303, 304
- Diffuse adenocarcinoma, 219, 227
- Diffuse colloid goiter, 43
- Diffuse erythema, 311
- Diffuse lymphocytic infiltration, 267
- Diffuse toxic goiter, 202 207, 271, 274, 281
 acute nonexophthalmic goiter, 205
 acute toxic goiter, 203, 206
 Basedow's disease, 206
 causation of signs and symptoms 274
 columnar epithelium, 204
 cuboidal epithelium, 206 207
 epithelial overgrowth, 203
 exophthalmic goiter, 205
 exophthalmic type of hyperthyroidism, 203
 follicular hyperplasia, 204
 formation of nodules, 206
 Graves constitution, 206
 Graves disease, 203
 Hertzler, 203 206
 histologic criterion, 206
 hyperplastic epithelium, 204
 hyperplastic primitive lymph nodes, 206
 involutionary nervous system 274
 lymph follicles, 204
 lymphoid constitutionality, 206
 Lugol's solution, 204, 274
 ocular signs, 276
 papillary infolding, 203
 papillary hyperplasia, 204 205, 207
 primary hyperthyroidism, 204
 pseudocapsule, 207
 W'arthin 204, 206
- Diffuse non toxic goiter, 201 202
 alveoli, 202
 anoxemia of cells, 202
 colloid retention, 202
 cuboidal epithelium, 202
 cystic degeneration, 202
 deposition of colloid, 201
 distention of acini, 202
 follicles, 202
 functional hyperplasia, 202
 interacinous adenomas, 202
 intrathoracic goiter, 202
 papillary adenomas, 202
 prepuberty to late adolescence, 201
 vacuolization, 202
- Digitalization, preoperative 387
- Dihydrotachysterol, 297
- Diiodothyronine* 105 106
- Diiodotyrosine, 93, 105 106
- Diiodotyrosine like fractions 94
- Dinsmore*, R S, 334 339 409, 415
- Discharge of intrafollicular colloid, 83
- Discrete adenoma, 209 342, 360 365
 capsule opened and enucleation, 365
 clamps, 361 362
 cutaneous nerves, 361
 damage to recurrent nerve 262
 enucleation, 366
 exposure before enucleation 364
 fascial plane, 361
 lobectomy, 364
 malignant degeneration of benign adenoma, 363
 nodules in contralateral node, 363
 removal, 361, 365
 Slaughter, 364
 subtotal thyroidectomy, 364
 trianguloid area to be avoided during dissection, 363
 unilateral non toxic adenoma, 364
 Ward, 364 365
- Dissociated tissue alveoli, 55
- Distant metastasis, 367
- Distention of acini, 202
- Distribution of endemic goiter in U S 114
- Disturbance of ocular muscles 413-414
 isolated muscle paralysis, 413
 Ruedemann 413
- Divisions of superior thyroid artery, 70
- Dixon*, C F, 333 334, 339
- Drxon*, J L, 398
- Dobyns*, B M 409-410, 413, 415
- Dockerty*, M B, 58, 63
- Dodds*, E C, 131, 146
- Dogliotti*, G G, 82, 286-287, 298

- Dorsum of the tongue, 18
 Dosage, 154, 188 189
Bartels, 155
Chapman and Evans 189
Hamilton, 188
Hamilton and Laurence, 188
Hertz and Roberts 188
Hertz, Roberts and Salter 189
 irradiation by x rays, 189
 potassium iodide, 155
 radioactive isotopes of iodine, 189
 thiouracil, 154
 Downgrowth of thyroglossal tract, 36
Downing V 195
 Drainage of deep mediastinal pockets, 370
Drill V A 306, 327
 Drug fever, 157
Du Bois E F 289, 298
Dunhill T P 32, 61
Dunn, T B, 89
 Duration of preoperative medication, 155
Van Winkle 155
 Dwarfism, 95
 Dyscrasias, 34, 13
 Dyspnoea, 18, 41

E

- Eaton, J C* 312, 327
Eberts, E M 217, 239
 Ectopic masses 26
 Ectopic thyroids, 51
 Edema of parathyroids, 398
 Effects on circulatory system, 99
 cardiac irritability, 99
 hyperthyroidism, 99
 hypothyroidism, 99
 Lerman, 99
 Effects of cold, 81
 abolished by hypophysectomy, 81
 section of pituitary stalk, 81
 Effects on human beings, 151
 Effects on nervous system, 98-99
 cerebral cortical alpha, 99
 cerebration, 98
 during hypofunction, 98
 emotional instability, 98
 electroencephalogram, 98
 in hyperthyroidism, 98
 irritability, 98
 in myxedema, 98
 nervousness, 98
 sensory acuity, 98
 thyroid administration, 99
 Effects of previous iodide therapy, 154
 Effects on serum cholesterol, 99 100
 combustion of lipid, 100
 in hyperthyroidism, 100
 hypofunction, 99
 Wilkins and Fleischman, 100
 Effects of thyrotropic hormone, 80
Engenberger, H 67, 89, 117
Eggerth A H, 279, 282
Eichorn K B 180, 182, 197
Eisen, D, 239, 264, 272
Essler, B, 130, 148
 Elasmobranch fish, 29
 Electrocardiographic abnormalities, disappearance under thyroid medication, 321
 Element 85, aka iodine, 194 195
 accumulation in thyroid of animals, 195
 Hamilton 194
 Hamilton and Soley, 194 195
 in non toxic goiter, 194
 therapeutic significance, 195
 Elevation of temperature, 386
Elliot R H. E. Jr, 165
Elman, R, 306, 327
Elmer A W 117, 137, 146, 196
 Embryonal cell groups, 59
 Embryonal or fetal adenoma, 212
 Embryology, x, 26
 aberrant thyroids, 26
 clinical significance, 26
 lateral aberrant thyroids, 26
 Embryology of the thyroid in lower vertebrates, 27
 amphibians, 27
 birds, 27
 fishes, 27
 isthmus, 27
 pharyngeal epithelium, 27

- reptiles, 27
- thyroglossal tract, 27
- Embryology of the thyroid in man, 30-31
 - alveoli, 31
 - anterior mediastinal space, 31
 - arch mesoderm, 30
 - branchiogenic pharynx, 30
 - cephalocaudal sequence, 30
 - ciliated epithelium, 31
 - endoderm, 30
 - endothelium, 30
 - eighth fetal week 30 31
 - fifth fetal month, 30
 - fifth fetal week, 31
 - follicle lumina, 31
 - foramen cecum, 30 31
 - isthmus of thyroid, 31
 - median diverticulum, 30
 - median primordium, 31
 - mesoderm, 30
 - pharyngeal pouches, 30
 - second month of intrauterine life, 31
 - sixth fetal month, 31
 - thyroglossal duct, 30 31
 - thyroglossus tractus of His, 31
 - tuberculum impar, 30
 - ultimobranchial body, 31
 - vascular mesenchyme, 31
- Embryonic rests, 26
- Embryonic thyroid tissue, 51
- Embryonically misplaced thyroid tissue, 52
- Emge, L A* 56 57, 61
- Emotional stresses, 393
- Endemic cretinism, 15, 17, 20, 106
- Endemic goiter, 14, 16, 20, 104 105
- Endocrine system, 101-102
 - athyreosis, 102
 - hyperactivity, 102
 - hypophysectomy, 102
 - involution of the pituitary, 102
 - involution of the thyroid, 102
 - pituitarectomy, 102
 - relation to pituitary, 101
 - Rogowitsch, 102
 - thyrotropic extract, 102
- Endothelial cells, 79
- Engelstead R B* 195
- Enright, L*, 117
- Enucleation, 412
- Enzymic digestion, 92
- Epidermoid carcinoma, 229
- Epileptiform convulsions, 396
- Epinephrine, 102, 275, 393
 - administration 393
 - and asthmatic seizures, 279
- Epiphyseal cartilage, 95
- Epithelial cells, 78
- Epithelial malignant tumors, 210
- Epithelial overgrowth, 203
- Epithelial proliferation in old age, 286
- Eppinger*, 278
- Erb's sign, 397
- Erdheim J* 61
- Errors on operating table 358-359
 - air embolism 359
 - collapse of trachea 359
 - damage to recurrent nerve, 359
 - hemorrhage, 359
 - pulse rate during anesthesia 359
 - thyroid crisis 358
- Esophageal artery, 72
- Esophagus, 69
- Essential hypertension 303 319
- Ether, 329, 334-335
 - Adams and Dixon, 334
 - cyclopropane ether, 335
 - ethylene ether, 335
 - Horton, 335
 - induction with gaseous agent, 335
 - maintenance anesthesia, 335
 - Nicholson, 334
 - Welch, 334
- Ethylene and ether, 335
 - ether anesthesia, 335
 - Lahey clinic, 335
 - Nicholson, 335
- European contributions, 14
- Eustachius, B, 15, 22
- Etans, H M*, 60, 62, 196
- Etans, R D*, 167, 187, 189, 192 193, 195, 197 198, 200
- Eversole, W H*, 331, 339
- Ewing, J*, 55, 59, 253, 264 265, 271 272

Excessive toxicity, 358
 Exfoliated acinar epithelium, 245
 Exophthalmic goiter, 4, 15, 18, 21, 98, 172, 205, 207, 271, 274, 281
 basal metabolic rate increase 279
 Bernard, 276
 capsule of Tenon, 276
 Chauffard and Giroit, 276
 causation of signs and symptoms, 274
 contraction of levator palpebrae superioris, 276
 contraction of Mullerian muscle fibers, 276
 gastro intestinal symptoms 280
 Hyman and Kessel, 275
 involutionary nervous system, 274
 iodine medication, 311
 Lugol's solution 274
 Maurice, 276
 ocular signs, 276
 origin of tumor, 280
 overactivity of suprarenal capsule, 276
 signs of von Graefe, Stellwag and Moebius, 276
 stimulating inferior cervical ganglia 276
 symptoms referable to thyroid, 281
 tachycardia, 277
 vasomotor symptoms, 280
 Exophthalmic type of hyperthyroidism, 203
 Exophthalmos, 4, 5, 275, 409-414
 anterior luxation, 411
 Antuitrin T, 413
 Barr and Shorr, 410
 Brain, 413
 causative factors in malignant exophthalmos, 413
 desiccated thyroid, 410, 412
 Dobyns, 409, 413
 Dobyns and Harnes, 409, 410
 enucleation, 412
 Hurtel exophthalmometer, 409
 hyperophthalmopathic Graves disease, 412
 iodine, 410

 malignant or progressive exophthalmos, 411, 413
 Mayo clinic, 409
 Means, 411-413
 Naffziger, 412
 Poppen, 412
 Ruedemann, 411-413
 Soley, 409
 tarsorrhaphy, 412
 thiouracil, 410
 thyroid extract, 412
 venous engorgement, 411
 Williams and Bissell, 410
 Extension of infection, 386
 Extensive miliary tuberculosis, 243
 Extensive pulmonary metastases, 185
 External capsule, 68
 External carotid artery, 70, 71
 External thyroglossal fistulae, 42
 Extirpation of cervical lymph nodes, 235
 Extracapsular finger dissection, 368
 Extraglandular fibrosis, 250

F

Fabricus Aquapendente, 3
Fagge, C. H., 16, 23
 hypothyroidism, 16
 sporadic cretinism 16
 False aberrant thyroids, 36
 circular, 36
 intrathoracic or substernal, 36
 retrolaryngeal, 36
 retrotracheal, 36
 subclavicular, 36
 False goitrous tumors, 36
Falta, M., 318, 327
Farrant, 241
 Fascial plane, 344, 361
Fashena, 131
 Fat droplets, 82
Femblatt, H. M., 279, 282, 320, 327
Fenger, F., 117
Ferris, E., 166, 196
Ferrer, M. I., 164
Ferry, 106
Fertman, M. B. 105, 117, 134, 145, 172, 173

- Fetal acini, 210
 Fetal adenoma, 12 13, 35, 48, 59 60, 216
 adenocarcinoma, 59 60
 carcinoma, 59 60
 colloid goiter, 59
 gelatinous adenoma, 59
 embryonal cell groups, 59
 Ewing, 59
 from adult follicles, 60
 Langhans, 59
 malignant, 12, 59
 papillary fetal adenoma, 60
 superfluous embryonal thyroid epithelium, 59
 thyroid epithelial tumors 58
 Wölfler, 59
 Fetal parenchyma, 35
 Fetal rest, 51 52, 208
 Fetal thyroid tissue, 50
 Fever, 311
 Fibrillation, 8
 Fibrosarcoma, 220, 231
 Fibrosis, 48 49, 193, 241, 246
 and calcification, 202
 Fibrous septa, 76
 Fibrous tissue proliferation, 77
 Fibrous trabeculae, 263
 Fiehe, W, 19, 23
 Fishberg, A M, 322, 327
 Fiske, F A, 398
 Fitzgerald, R R, 142, 144, 239, 311, 328
 Flajani, Giuseppe, 18 19, 23
 Flaxman N, 399
 Flaxseed poultices, 386
 Fleischman, W, 100, 119, 139, 146
 Fluids, 395
 Focal infection in rhinopharyngeal tract, 282
 Foderé, F E, 23
 Foldes, F F, 196
 Follicular hyperplasia, 204
 Follicular type of fetal adenoma, 208
 Follicles, 202
 Folliculoma malignum ovarii, 56
 Foramen cecum, 48, 50
 Forbes, J C, 139, 146
 Formation of nodules, 206
 Forsythe, R, 61
 Foss, H L, 398
 Foulger, 149
 Fourth pharyngeal pouch, 53
 Fowler, C H, 75, 89
 Fox, E L, 18 23, 92
 Fox N, 250, 271
 Frank carcinoma, ix
 Frankl, 58
 Franklin, A L, 164, 169, 174, 196, 200
 Frantz V K, 42, 53 61 182 184, 196, 198
 Frequency of occurrence of postoperative hyperthyroidism, 401
 Friedgood, H B, 123 124, 146
 Fulminating malignant lesions of thyroid gland, 228
 Functional fetal tissue, 60
 Functional hyperplasia, 202
 Functional ovarian strumas, 58
 Future of thyroid surgery 418-424
 circulatory failure, 418
 concentration of circulating hormone 418
 diagnostic significance, 418
 differential diagnosis, 421
 discovery of one or more toxic products, 423
 discrete adenomas, 420
 functional metastases from cancer of the thyroid gland, 422
 exophthalmic goiter, 423
 geriatric patient, 418
 goitrogen therapy in exophthalmic goiter, 421
 Graves disease, 419
 iodination, 420
 isotopes, 423
 lateral aberrant thyroids, 422
 methods of determining serum iodine level, 418
 methods of diagnosis and of estimating operability and degree of thyrotoxicosis, 418
 methods of management, 419
 mortality rate, 418

- nomenclature, 421
 חלח חלח tumors, 421
 חלח חלח thyroacilization, 421
 חלח חלח iodine, 422
 חלח חלח after thyroacil therapy,
 חלח חלח
 חלח חלח to thyrotoxicosis, 424
 חלח חלח ethical considerations, 424
 חלח חלח crisis, 423
 חלח חלח nodular goiter, 423

G

- Galactose tolerance test, 302
Galen 15
 Gallbladder, 45
Garaui B., 287, 289, 298
Gargill S. L. 164, 415
Garlock, J. H. 356, 358, 381
Garnier, 241
 Gastro intestinal symptoms, 280 281
 acidity of gastric juice, 281
 vomiting and diarrhea, 281
Gay Lussac 111
 Geiger counter, 183 184, 186
 Geiger Müller counter, 166, 178-180,
 187
 Gelatinous adenoma 59
Gellhorn E., 392, 399
 General anesthesia in aged, 296
Gerard G. W., 392, 398
 Geriatrics, 284
Gerl A. J., 164
Germane H. M. x, 259 260
 Gerontology, 284
Gersh, I. 83, 89
Getzoua, S. 61
Ghigi, C. 287, 298
 Giant cell carcinoma, 229
 Giant cell variant of struma fibrosa
 250
 Gigli saw, 371
Gildea E. F., 132, 146
Gillette, N. W., 416
Gilmour J. R., 61
Giordanengo, G., 247, 261
Givot, L., 276, 282
 Gland weight, 104
 Glandular arteries, 70 72
 large posterior branch, 72
 small anterior branch 72
 Glandular hyperplasia, 275
Gley, M. E. 17, 23
 Glycerine extract of sheep's thyroids
 18
 Glycosuria, 320
Godum, M. C. 31 35, 61
Goetsch, E., 196, 252, 271
 Goetsch test, 102
 Goiter in adolescence, 311
 Goiter heart, 322-326
 analysis of heart sounds 323
 auricular fibrillation and flutter, 324
 cardiac hypertrophy, 323
 cardiac lesions, 323
 cardiac weakness 324
 clinical observation 324
 congenital anomalies, 322
 enlargement, 324
 hypertrophy of left ventricle, 323
 myocardial disease, 326
 myocardial injury, 324
 pathologic study, 323 324
 systolic murmurs, 323
 tachycardia, 322
 valvular defects, 323
 x ray examination, 324
 Goiter mobile, 42
 Goiter plongeant, 36
Goldblatt H. 254 255, 272
 Golgi net, 82
Goldzieher M. A., 284 285, 289, 298
Goodale 271, 273
Gorbman A. 60, 62, 196
Gottschalk 56
Graham, A. 214 220, 239, 247, 253,
 266 268, 270, 272, 366, 381
 Granulocytopenia, 156 157
 Grave toxemia, 212
Graves R. J., 19, 23
 Graves constitution, 110, 206
 Graves disease, 123 127, 129, 133,
 138 142, 145, 158, 178 179, 185,
 187, 203, 308, 312, 319 321
 Graves disease and glycosuria, 321
Gray, 241

Greene, E I, 292, 295, 299
 Greenbill, J P, 117
 Greteman and Russum, 52
 Griesbach, W E, 89
 Gross, H T, 328
 Gross, J, 198
 Gross anatomy, 66 68
 accessory thyroid glands, 66
 Boyd, 67
 Castaldi, 67
 Eggenberger, 67
 Guiart, 67
 Hellwig, 66 68
 'moderately goitrous' region, 66 67
 Jaffé, 67
 Klöppel, 67
 Marine, 67
 Nolan, 67
 in "non goitrous" region, 66
 Rice, 66 67
 Von Kolnitz and Remington, 67
 W'egelin, 67
 weight in adults, 67
 weight at birth, 66
 Grosser, O, 33, 35, 51, 64
 Growth of nails and hair, 96
 Grüber, W, 35, 39, 62
 Guiart, 67
 Gull, W W, 16, 23, 92
 Gull's disease, 16
 Guptill, P, 311, 328
 Gusberg, S B, 56, 58, 62
 Guthrie, D, 370, 381
 Gutman, A B, 123, 196

H

Haagensen, 215
 Hemostats on branches of inferior artery and vein, 350
 Haines, S F, 103, 117, 119, 321, 328
 339, 404, 409-410, 416
 Hall, A R, 89
 Haller, 42
 Hamilton, F E, 89
 Hamilton, J G, 84, 89, 168-169, 175,
 178 182, 186, 188, 194 195, 197
 Hamilton, W J, 62

Handbook of Nutrition 20
 Händel, M, 319, 328
 Hanford, J M, 61
 Hanson, W A, 75, 89
 Hardy, S, 165
 Hare, H F, 217, 234, 236 237, 239
 Harrington, C R, 93 94, 106, 117,
 171, 197
 Harry, N M, 247, 253 255, 272
 Hashimoto, H, 247, 264 266, 272
 Hashimoto's disease (struma lymphomatososa), 11-13, 242 250, 263-271
 absence of obstructive symptoms,
 265
 acinar epithelium, 263
 adrenal cortical insufficiency 268
 alveoli, 263
 bacterium, rickettsia or virus 268
 chronic lymphoid thyroiditis 11
 clinical picture, 263
 comparison with Riedel's struma
 265
 cut surface, 263
 DeCourcy, 269
 diffuse lymphocytic infiltration 267
 distinct from Riedel's struma, 264
 Eisen, 264
 Eisenharte struma, 265
 fibrous trabeculae, 263
 followed by productive fibrosis and
 scar tissue formation, 266
 germinal centers, 12
 Graham, 266 268, 270
 Graham and McCullagh, 264, 266
 Hashimoto 264 266
 Hertzler 264, 266 267
 infiltration with connective tissue
 265
 Joll 264, 266 268
 Lee, 264
 Lee and McGrath, 264
 lymphadenoid goiter, 265, 268
 lymphoid overgrowth, 263
 lymphoid tissue, 12
 Marine, 270
 McCarrison, 268
 McClintock and Wright, 264, 271
 McSwain and Moore, 264, 267, 269

- Moore and Lloyd*, 264
 multinuclear giant cells, 12
 relative lymphocytosis, 264
Renton, 271
Riedel, 265
Riedel's struma, 266-270
Scarcello and Goodale, 271
struma lymphomatosa, 265
 subtotal thyroidectomy, 12
 surgery, 12
 tendency toward postoperative
 hoarseness, 265
 vascularity, 263
Williamson and Pearse, 264-265
Womack, 264, 268, 270
Hashimoto's struma, 159
Hazel, G. R., 165
Heart, 322
 Heat flashes, 323
Heggie, J. F., 273
Hellwig, C. A., 66-68, 78, 87, 89, 242,
 247, 254, 272
 Hematoma, 385
 Hematopoiesis and the thyroid, 99
 Castle, 99
 Jaffé, 99
 Lerman, 99
 myxedema, 99
 pernicious anemia, 99
 sclerosis of the gland, 99
 severe anemia, 99
 Hemorrhage, 385, 393
 Hemostasis, 369-370
Hendrick, J. W., 293, 295, 298
Henke, F., 91
 Hepatic difficulties, 386
 Hepatic insufficiency, 307
Hercus, 149
Herdle, E., 328
 Hereditary neuropathic disposition, 19
Herrmann, G., 33, 62
Hertoghe, 103
Hertz, S., 167-168, 175, 177-181, 186-
 193, 197-198, 306, 328
Hertzler, A. E., 77, 84-86, 89, 203-
 208, 235, 239, 244, 248-249, 255,
 264, 266-267, 284, 287-289, 294,
 298
Hess, 278
Higgins, C. C., 75, 89
Himsuorth H. P., 164
Hines, D. C., 165
Hinton, J. W., 76, 89, 91, 146, 210,
 214, 239, 298
 Hippuric acid test, 302
Hiss, W., 31-32, 62
 Histology and cytology, 76-77
 connective tissue septa, 76
 fibrous septa, 76
 fibrous tissue proliferation, 77
 interlobular stroma, 76-77
 lobules, 76
 perifollicular septa, 76
 septal primary lobules, 76
 Histopathological classification, 214
 Historical aspects, 11
 Historical background, vii
 History, 3, 111
 Chatin, 3
 Fabricius Aquapendente, 3
 Kendall, 3
 Marrine, 3
Hutchcock F. A., 117
Hodge, H. C., 195
Hoer, A., 118
Holmes G. W., 199
Holst, J., 131, 146
 Homolateral anastomosis, 71
 Homolateral inferior thyroid artery, 70
 Homolateral lobe, 33, 51
Hoover W. B., 61, 399
 Hormonal iodine, 132
 Hormone production, 123
 Hormone storage, 3
Horsley V., 16-17, 23
Horton, J. W., 175, 335, 339
Hoskins, R. G., 15, 62
Hughes, A. M., 163
Huguenin, R., 217-218, 232, 240
Hume, E. H., 23
Hunt, M. F., 298
Hunt, T. E., 89
 Hurler exophthalmometer, 109
 Hürthle-cell tumor, 183, 219
Hurxthal, L. M., 118
Hutchinson, 93

- Hyaline degeneration and hemorrhage, 49
- Hyaline stroma, 87
- Hyalinization of the stroma, 257
- Hyman, H T*, 275, 282
- Hyoid, 36, 72
- Hyoid bone, 26, 36, 48, 50
- Hyperactivity, 102
- Hyperextension of neck, 330
- Hyperexophthalmopathic Graves disease, 412
- Hyperfunction, vii, 5, 13, 110
 acromegaly, 110
 emotional instability, 5
 etiologic factors, 110
 flushing of the skin, 5
 Graves constitution, 110
 Graves disease, 5
 hyperpituitarism, 110
 hyperplasia, 5
 increased metabolic rate, 5
 increased pulse rate, 5
 loss of physical strength, 5
 loss of weight, 5
 nervousness, 5
 response to iodine, 110
 symptoms and signs, 110
 tachycardia, 5
Thompson, 110
 thymicolymphatic constitution, 110
 thyroid enlargement, 5
 toxic diffuse goiter, 5, 13
 toxic goiter, 110
 toxic nodular goiter, 5, 13
 tremor, 5
Warthin, 110
- Hyperpituitarism, 110
- Hyperplasia, 36
- Hyperplastic, 10
 epithelium, 204
 goiter, 5, 123
 primitive lymph nodes, 206
 thyroid, 93
 thyroid neoplasms, 158
 tissue, 50
- Hypertension, 320
- Hypertension and hyperglycemia associated with exophthalmic goiter, 321
- Hyperthyroid, ix
- Hyperthyroidism, 4 5, 7 8, 18, 20 21, 57, 291-294
 in aged, 291
 adenomatous goiter, 293
Bram, 292 293
 cardiac complaints, 294
 circulatory disorders, 294
Crile, 292
 diagnosis of thyrotoxicosis, 294
 eye findings, 294
Hendrick, 293
Hertzler, 294
 masked hyperthyroidism, 294
 mental confusion or psychosis, 294
Mora and Greene, 292
 most frequent symptoms, 293
Plummer, 293
 sex incidence of Graves disease, 292
 symptoms, 292
- Hyperthyroidism at menopause, 270
- Hyperthyroidism in pregnancy 60, 111
 abortion, 11
 blood iodine, 111
 nursing, 111
- Hypertrophic parenchymatous thyroid, 207, 210
- Hypertrophy of the adrenal cortex, 102
- Hypertrophy of media, 256
- Hypertrophy and hyperplasia of follicular epithelium, 245
- Hypodermoclysis 307
- Hypofunction, vii, 13, 106-108
 of adrenal medulla, 102
 cretinism, 13, 106
 cretinoid facies, 107
 endemic cretinism, 106
 myxedema, 13, 107-108
 anemia, 108
 basophilia, 108
 blood changes, 108
 blood iodine, 108
 calcium metabolism, 108
 chloride level, 108
 circulatory changes, 108
Curtis, 109
 electrocardiographic changes, 108
 eosinophilia, 108

- etiologic factors, 108
 - increased bicarbonate, 108
 - increased heart size, 108
 - lowered cardiac efficiency, 108
 - menstruation, 108
 - myxedematous infiltration of cardiac musculature, 108
 - paradoxical hypothyroidism, 107
 - protein content of cerebrospinal fluid, 108
 - serum cholesterol level, 108
 - symptoms, 107
 - volume of the heart, 108
 - spontaneous myxedema, 108
 - Hypometabolism in later life 289-291
 - Antschkow* 290
 - atherosclerosis of aorta in rabbits, 290
 - basal heat production, 289 291
 - Benedict*, 289
 - Boothby and Sandiford* 289
 - Bruger and Rosenkrantz*, 289 290
 - Carlson*, 289
 - Clerc*, 289
 - Clinical practice of geriatrics, 291
 - Cooper*, 289
 - degeneration of thyroid, 291
 - DuBois*, 289
 - Hertzler*, 289
 - Leuts*, 289
 - Liebig*, 290
 - Marine* 290
 - McCarrison*, 289-290
 - Page*, 290
 - relationship between hypercholestermia and atherosclerosis, 290
 - Seel and Kreuzberg*, 290
 - Turner*, 291
 - value of thiouracil and other goitrogenic substances, 290
 - Hypoparathyroidism, 396-399
 - transient and chronic, 397
 - Hypophyseal activity, 79
 - Hypothyroidism, ix, 4, 398
 - cretinism, 4
 - myxedema, 4
 - therapeutic use of thyroid substance, 291
 - Hypothyroidism secondary to pituitary dysfunction, 101
- ## I
- Iason, A H* 128 146
 - Idiocy, 17
 - Imbalance, vii
 - of sympathetic nervous system, 393
 - Importance of periodic examinations, 414
 - anemia, 414
 - basal metabolic rate, 414
 - Boenheim*, 414
 - electrocardiogram, 414
 - hemoglobin, 414
 - Inanition, 97
 - Inadequate sedation, 383
 - Incidence of different histopathological types, 219
 - Incidence and geographical region, 217
 - Incidence of recurrent hyperthyroidism, 403
 - Incipient carcinoma, ix
 - Incision along posterior border of lateral cartilage and inferior cornu, 389
 - Incision of sternum, 11
 - Increased appetite, 18
 - Increased consumption of food, 19
 - Increased prominence of the eyes following medical and surgical treatment, 409
 - Increased rate of protein metabolism, 19
 - Indirect anastomosis, 71
 - Indirect communicating channels 71
 - Infections, 307, 385, 393
 - Inferior constrictor, 68, 70, 72
 - Inferior laryngeal artery, 71-72
 - Inferior maxilla, 55
 - Inferior parathyroid body, 69
 - within or posterior to the fascial sheath, 69
 - Inferior pole, 71
 - Inferior thyroid artery, 69, 71 72
 - Inferior thyroid veins, 68
 - Infiltration of lymphocytes, 49

- Inflammations, 13
 Influence carbohydrate metabolism, 98
 Informal psychotherapy, 305
 Infrahyoid artery, 70
 Inhalation anesthesia, 333
 Innominate artery, 72
 Insertion of sternothyroid into oblique line of lamina, 68
 Interacinous adenomas, 202
 Interacinar connective tissue, 85
 Interfollicular cells, 85 86
 Andrew and Andreu, 86
 budding, 85
 in childhood, 85
 clumps of cells, 86
 developing acini, 86
 diffuse or nodular lymphatic tissue, 85
 fetal rests, 85
 Hertzler, 85 86
 interacinar connective tissue, 85
 interfollicular epithelial cells, 85
 mature acini, 86
 migration of argyrophil, 86
 old age, 85
 parathyroid tissue, 85 .
 puberty, 85
 Rice 85
 tangential sections 85
 Thomas, 86
 thymic tissue, 85
 true parafollicular cell nests, 86
 young adult, 85
 Interfollicular epithelial cells, 85
 Interlobular arteries, 70
 Interlobular stroma, 76 77, 87
 Internal capsule, 68
 Internal mammary arteries, 71 72
 Interstitial edema of fibers, 101
 Intracellular granules and cell inclusions, 81 83
 centrosome, 81
 cytoplasm, 81
 fat droplets, 82
 Golgi net, 82
 mitochondria, 81
 relation to metabolism, 81
 Intracystic papilliferous adenoma of thyroid, 223
 Intrafollicular colloid, 83 85
 absorption of ultra violet light, 83
 acidophilic colloid, 84
 administration of potassium iodide, 84
 after fixation, 83
 Altmann Gersh freezing drying technique, 83
 Andrew and Andreu 84 85
 basophilic colloid, 84
 denser eosinophilic, 84
 De Robertis 83 84
 first appearance, 84
 Hamilton, 84
 Hertzler, 84
 injection of thyrotropic hypophyseal hormone, 84
 inversion of cell polarity 84
 Kingsbury, 84
 Leblond, 84
 Lelkes 84
 Norris, 84
 radio iodine, 84
 in senile gland, 85
 unhomogeneity, 84
 vacuolization, 85
 young adult, 83 84
 Intralobular arterioles, 70, 73
 Intrathoracic extensions, 293
 of malignant adenoma, 268
 in old age, 293
 Intrathoracic goiter, 42 48, 202 342
 368-372, 386
 adenomas, 43
 adenomatous goiters, 43
 alveolar tissue, 43
 aneurysms of the aorta, 45
 anteriomediastinum, 45
 attached to the pericardium, 47
 benign metastasis, 43
 closure, 371
 complete, 42
 cysts, 48
 DeCourcy, 368
 deviation of trachea, 45
 diffuse colloid goiter, 43

- drainage, 370
 - of deep mediastinal pockets, 370
- dyspnea, 11
- electric circular saw, 371
- extracapsular finger dissection, 369
- first degree, 42, 369
- fixed, 42
- gallbladder, 15
- Gigli saw, 371
- goiter mobile, 42
- Guthrie and Schimmel* 370
- Haller*, 42
- hemostasis, 369
- intrathoracic tumors, 43
- intravenous glucose solution, 47
- Lahey* 370
- Lugl*, 42
- low collar incision, 43
- Means*, 43
- mediastinum, 43, 45
- mobile, 12
- obstructive symptoms, 372
- partial, 12
- prethyroid muscle, 43
- related to the pericardium, 48
- removal of, 368
- retrosternal goiter, 12
 - removal of, 371
- Schreff*, 42
- splitting the sternum, 43
- spring goiter, 12
- subclavicular goiter, 42
- substernal approach, 371
- substernal goiter, 12
- third degree, 41
- thoracic approach, 371
- true aberrant intrathoracic goiter, 13
- wandering goiter, 42
- Intrathoracic tumors, 43
 - in deviation of, or pressure on, trachea, 331
- Eversole*, 331
- examination of vocal cords, 331
- intratracheal intubation, 331
- preliminary sedation, 332
- roentgenograms of neck and chest, 331
 - in thyroid operations on children, 331
- Intratracheal catheter, 367
- Intravenous amino acid alimentation, 306
- Intravenous anesthesia, 336
 - laryngeal reflexes, 336
 - Nicholson*, 336
 - pentothal sodium, 336
- Intravenous glucose solution, 47, 333
- Intravenous instillations, 395
- Intravenous pentothal, 333
- Involuted Graves type thyroid, 212
- Involution of the hyperplastic glands, 125
- Involution of the pituitary, 102
- Involution of the thyroid, 102
- Iodide therapy, 154
- Iodine, 10, 16, 18, 142-145, 179, 410
 - loss, 179
 - medication in thyrotoxicosis, 142
 - DeCoursey* 142
 - Fitzgerald*, 142, 144
 - Graves' disease, 142, 145
 - Kocher* 142
 - Lugol's solution, 143-144
 - Means and Lerman*, 145
 - nodular goiter with toxicity, 144
 - Plummer*, 142
 - treatment after operation, 144
 - value of iodine administration, 142
- metabolism as affected by iodine therapy, 122
- metabolism and blood iodine, 121-179
 - after hypophysectomy, 126
 - analyses of blood and urine, 178
 - analysis of radioactive material in blood, 179
 - analysis of thyroid tissue after operation, 179
 - basal metabolic rate, 178
 - blood iodine, 132
 - blood iodine determinations, 141
 - blood iodine level in non-toxic nodular goiter, 134
 - blood iodine levels, 121

- in carcinoma of the liver, 137
- in chronic cholecystitis, 137
- Cole and Curtis*, 139
- common duct ligation, 137
- Curtis*, 130
- Curtis and Fertman*, 134
- Danowski*, 135 136
- DeCourcy*, 121 122, 131, 136 137
- DeCourcy clinic, 136
- decrease in height of thyroid epithelium, 128
- determination of the alcohol in soluble iodine of blood, 131
- determination of serum iodine levels, 132
- detoxifying function in hyperthyroidism, 139
- Dodds*, 131
- dosage ceiling, 179
- Elmer and Luczynski*, 137
- exophthalmic goiter, 122
- Fleischmann and Schumacker*, 139
- Forbes*, 139
- Friedgood*, 123 124
- Geiger Muller counter, 178 179
- Graves disease, 123 129, 133, 138, 178 179
- Gutman*, 123
- Hamilton*, 178 179
- Hamilton and Soley*, 179
- Hertz*, 178
- Hertz, Roberts, and Salter*, 179
- histologic study, 178
- Holst and Lunde*, 131
- Iason*, 128
- involuting action of iodine, 128
- iodine loss, 179
- iodine medication in thyrotoxicosis, 142
- iodine metabolism as affected by iodine therapy, 122
- iodine metabolism in relation to liver function and reticuloendothelial system, 136
- Journal of Endocrinology*, 127
- Kupfer cells, 139, 141
- Lahey clinic, 131, 137
- level of serum precipitable iodine, 121
- liver function, 121
- liver death, 141
- Lugol's solution, 122
- Lunde*, 147
- Marine*, 122
- Maruno*, 137, 139
- McCullagh*, 130
- McCliver and Winter*, 138
- Means*, 127
- Means and Lerman*, 123 124
- metabolic response, 178
- Morton*, 125 126
- noniodized patients with toxic nodular goiter, 128
- observations on animals, 178
- Perkin and Cattell*, 131, 133, 137
- Perkin Lahey and Cattell*, 131
- Peters and Man*, 139
- Plummer*, 122 124
- radioactive iodine, 125
- radio thyroxin, 126
- recurrent hyperthyroidism, 135
- reticuloendothelial tissue of liver, 133
- relative measurements of concentration of labeled iodine, 178
- Riggt*, 129
- Riggt, Gildea Man, and Peter*, 129
- Riggt, Man, and Winkler*, 128 132, 136
- role of liver in iodine metabolism, 132
- Salter*, 124
- Salter, Bassett, and Sappington*, 132
- Salter and Lerman*, 124
- Salter and McKay*, 132
- Scheffer*, 139
- Schittenhelm and Eisler*, 130
- serum cholesterol, 129
- serum iodine level, 132
- serum precipitable iodine, 129
- significance of blood iodine level, 129
- Simendinger*, 139

- simple colloid goiter, 122
- Stern*, 130
- Stein*, 137
- supranormal values for serum iodine, 131
- tachycardia, 122
- Talbot, Butler, Saltzman, and Rodriguez* 132
- Taurog Chukoff, and Bennett*, 126
- therapeutic use of radioactive iodine in Graves' disease, 179
- thiouracil treatment, 125
- toxic iodine-containing secretion, 127
- tracer dose, 178
- Tresorrou and Fashens*, 131
- Turner*, 130
- Turner, De Lamar and Prosser*, 132
- Weller*, 137
- Winkler*, 131 136
- Wohl*, 130
- X factor, 134
- X secretion, 122
- Yazuriba* 139
- Iodine metabolism in Graves' disease, 177
 - Hertz, Roberts and Salter*, 177
- Iodine prophylaxis, 20
- Iodine therapy, 21, 384
 - in cases of diffuse goiter with toxicity, 311
- Iodine and thyroid physiology, 104-105
 - Baumann*, 104
 - blood iodine, 104
 - carcinoma 105
 - colloid goiter, 104
 - Curtis*, 105
 - diiodotyrosine, 104
 - endemic goiter, 104 105
 - exophthalmic goiter, 104
 - Fertman*, 105
 - hyperthyroidism, 105
 - infection, 104
 - iodine content of thyroid, 104
 - iodine intake, 104
 - Kimball*, 105
 - lactation, 104
 - Marine*, 104
 - pregnancy, 104
 - puberty, 104
 - relative deficiency, 104
 - thyroxin, 104
 - toxic adenoma, 105
- Iodine thyrotoxicosis, 311
- Iodine treatment, 9
 - colloid, 9
 - distention of acini, 9
 - general circulation, 9
 - iodine fast, 9
 - mechanical block, 9
 - return of toxicity, 9
 - secretion of the cells, 9
 - stasis, 9
- Iodine with thio drug, 312-314
 - action of thiourea or thiouracil, 312
 - Bartels*, 312
 - Danowski*, 312-313
 - Danowski, Man, and Winkler*, 312
 - Eaton*, 312
 - Means*, 312
 - problem of postoperative hyperthyroidism, 314
 - Rauzon*, 312 313
 - Reteno*, 312
 - thiouracil and hyperplastic thyroid gland of Graves' disease, 312
 - Williams and Clute*, 312
- Iodized salt, 20
- Iodization, 308 310
 - Barker and Wood*, 311
 - DeCourcy* 309
 - Graves' disease, 312
 - Guptill*, 311
 - Kocher*, 308
 - Lugol's solution*, 309
 - Means and Lerman*, 312
 - Plummer*, 309
 - postoperative reaction, 310
 - reactions, 311
 - subtotal thyroidectomy, 309
- Iodized Salt Committee, 113
- Iodothyroglobulin, 93
- Iron hardness, 250

Irradiation of pituitary gland, 317
 Irritation of free mucous membranes
 311
 Isolated muscle paralysis, 413
 Isthmus, 15

J

Jaffé, R H, 67, 87, 89, 99, 118
Jandorf, B J, 151, 165
 Jaundice, 296, 386
Johnson, E C, 297, 337, 339
Joll, C A, 39, 50, 96 97, 243, 247,
 264, 266 268, 272 273, 277, 330,
 375
Journal of Endocrinology, 127
Joyce, T M, 416
Juvenal, 14
 Juvenile myxedema, 95

K

Kaan, H W, 89
Kastschenko, N, 32 33, 62
Kay, G A, 151, 165
Keating, F R, Jr, 174, 198
Kendall, E C, 3, 23, 93, 118, 278, 282
Kennedy, R L J, 218, 239
Kennedy, T H, 89, 149, 164
Kenney, F R, 165
Kessel, L, 275, 282
Kessler, M, 392, 399
Keston, A A, 196
 Kidney failure, 296
Kimball, O P, 105, 117
King, B T, 158, 164, 389
King J D, 89
King, T W, 17, 23
 thyrotoxin, 17
King, W L M, 54, 62
Kingsbury, B F, 33 35, 51, 64, 84,
 89
Klein, J, 89
Klöppel, F C, 67, 89
Knight, R T, 337 339
Kocher, T, 17, 23, 92, 142, 217, 239,
 243, 308, 328
Korenchetsky, V, 288 289
Körpen, Y, 27, 33

Krafka J, 62
 Kupfer cells, 139, 141

L

Lahey F H 53, 62, 75, 88, 131, 147,
 198, 212, 217, 236, 239, 298, 356,
 359, 367, 370, 381, 399
 Lahey clinic, 131, 335
Langendorff, 28 80
Langefeld, H, 118
Langhans, 59
 Langhans struma, 216
Langley, 280
Lansing W, 90, 288 289
Larson, R A, 171, 174, 198
 Laryngeal obstruction, 330
 Lateral aberrant cervical thyroids 54
 Lateral aberrant thyroid bodies, 342
Lateral aberrant thyroid tissue 374
 irradiated with voltage x rays 374
 malignancy, 374
 potentially malignant, 374
 radical neck dissection 374
 Lateral aberrant thyroids 26 51-55
 anomalous embryonic development,
 51
 benign lateral aberrant thyroid tu-
 mors, 54
 benign tumors, 53
 carcinoma, 54
 of the homolateral thyroid lobe
 54
Cattell 52
Clay and Blackman 54 55
 coexistence of carcinoma in the thy-
 roid proper, 53
Cohn and Steuart 52 53
 congenital cretinism, 53
Crile, 52 53
 cystic tumors, 51
 dermoid cysts, 56
Dunhill, 52
 ectopic thyroids, 51
 embryonically misplaced thyroid tis-
 sue, 52
 fetal rest theory, 52
 fourth pharyngeal pouch, 53
Frantz, 53

- Gretema and Russum* 57
Grosier 51
 homolateral lobe 51 54
 intrinsically malignant 52
King and Pemberton 54
Kingsbury 51
 lateral aberrant cervical thyroids 51
 lateral anlage (ultimobranchial body) 52
 lateral cornu of the median anlage 53
 lateral thyroid anlagen 51
Lou 51
 lymph follicles 54
 malignant aberrant thyroid lesions 51
 malignant growths 51
 malignant tumors 53
 marginal sinus 51
 median aberrant thyroid tumor 53
 median anlage 51
 metastases from primary tumor 51
 metastases in the cervical lymph nodes 54
 metastases to the cervical lymph nodes 53
 papillary carcinoma of the thyroid 54
 papillary cystic thyroid tissue 51
 papillary cystadenomas 52
 papillary nature 51
 papillary tumors 52
 papillomatous tumors 51
 precancerous 52
 primary tumor 52
Schragar 51
 sinusoids 54
 surgical removal of the primary lesion 53
 tumor of the homolateral lobe 57
 ultimobranchial bodies 51 52
Von den Hildenberg 52
Weller 53
Wohl 52 54
 Lateral anastomosis 71
 Lateral anlage (ultimobranchial body) 52
 Lateral cornu of the median anlage 53
 Lateral ducts 12
 Lateral lobe 69
 Lateral lymphatics 74
 Lateral thyroid anlagen 51
Lattetes P H 117
Laurence C H 118
Laurence J H 188 193 197 199
Lauson W 116
Lauton S E C 2
Lazarus J A 62
Leblond C P 81 90 173 177 198 199
Le Camus H 199
Lee C M 264 273
Lee J G 250 264 272 273
Leech J V 63
Lein A 198
Leitch I 119
Letter L 158 164 185 199
Lelkes Z 81 90
Lenhart C H 118 278 283
Lerman J 92 94 99 102 106 118 123 124 145 147 199 200 306 312 328
Lerner S R 164 170 196
Leses M F 164
 Leukocytes 245
 Leukopenia 157
 Levator glandulae thyroideae 33
Leime R 165 200
Leuss R A 97 118
Leuss W H Jr 283 288
Leib M M 282
Lebig H 290 298
 Ligation of superior artery 70
 Ligation of thyroid arteries 375 380
 damage to thyrotoxic thyroid tissue 379
DeCourcy 376
 demonstration of nerve 380
 division of deep fascia exposing muscle fibers and external jugular vein ligation 377
 double superior ligation 376
 of inferior artery 376 379
 inferior ligation 378
Joll 375
 margin of safety at operation 377

- Plummer*, 375
 scalenus anticus muscle, 379
 single superior ligation, 376
 of superior artery, 375
 transverse incision, 378
- Ligneous or woody thyroiditis, 247, 252
- Lingl*, 42
- Lingual artery, 72
- Lingual duct, 42
- Lingual thyroid, 48-51, 53
 anlage, 50
 calcium deposits, 51
 carcinoma, 51
 degenerative type of tissue, 50
 dorsum of the tongue, 48
 embryonic thyroid tissue, 51
 fetal rest, 51
 fetal thyroid tissue, 50
 fibrosis, 49
 foramen cecum, 48, 50
 hyaline degeneration and hemorrhage, 49
 hyoid bone, 48, 50
 hyperplastic tissue, 50
 infiltration of lymphocytes, 49
- Joll*, C A, 50
- median primordium, 50
- Montgomery*, 50 51
- parathyroid nodules, 50
- pharynx, 48
- suprahoid, 50
- suprahoid thyroid nodule, 50
- thyroglossal tumor, 50
- tuberculum impar, 51
- Lister*, 17
- Liver death, 141, 306
- Liver failure, 296
- Liver function, 20
- Lloyd*, O D, 264, 273
- Lobectomy, 364
- Lobular pneumonia, 48
- Lobules, 76
- Local anesthesia, 333-334
Adams and Dixon, 333-334
 in aged, 296
 blocking superficial cervical plexus, 334
- Dinsmore and Shively* 334
- metycaine, 334
- nitrous oxide and oxygen, 334
- in operations upon geriatric patients, 296
- procaine, 334
- procaine hydrochloride, 334
- regional, 333
- Local anesthetic, 343
- Loeb*, L 88
- Loeser*, A, 123 124, 146
- London Clinical Society 17
- London Royal Society, 16
- Longus capitis, 68, 70
- Lord*, J W 210, 214, 239
- Lord*, J W, Jr, 138, 146
- Lough*, W G 146
- Lovelace*, W R Jr, 227-228 236, 239
- Lou*, 51
- Low collar incision 43
- Low Beer*, B V A 199
- Louenstein* B E, 132, 146
- Lubarsch* O, 91
- Luczynski*, Z, 137, 146
- Lugol's solution, 10, 122, 143 144, 159, 204, 256, 260, 262, 274, 281, 309 310, 356
- Lunde*, G 131, 147
- Lyle*, Donald J, x
- Lymph follicles, 54, 204
- Lymph nodule with germinal center in early chronic lymphatic thyroiditis 264
- Lymphadenoid goiter, 265, 268
- Lymphatic or myelogenous leukemia 303
- Lymphatic systems of the thyroids and parathyroids, 69
- Lymphatics of the thyroid*, 74-75
 broadening of lymphatic channels 74
 cervical or internal jugular chain, 74
 colloid within lymphatic vessels, 74
 lateral lymphatics, 74
 medial lymphatics, 74 75
 paratracheal and deep cervical glands, 75

paratracheal and pretracheal glands, 75
 passageways for metaplastic growths 74
 prelaryngeal glandules, 74
 secretion from epithelial cells of follicles, 74
 superior mediastinal glands, 75
 thyrohyoid glandules, 74

Lymphocytes, 252

Lymphoid constitutionality, 206

Lymphosarcoma, 219, 230

M

MacBryde, C. M., 397, 399

MacKerzie, C. G. 18, 21, 23, 149, 164

MacKenzie J. B. 23, 119, 164

MacKenzie H. W. G. 23

Macular papular dermatitis, 311

Maddock, W. G., 392, 399

Madison R. K. 199

Magnus Levy, A. 19, 23, 93

Mahorner H. R., 90

Malignancy, 36

Malignant aberrant thyroid lesions, 54

Malignant adenomas 216, 219-220, 365-368

anaplastic carcinoma, 368

benign adenoma, 35, 220

benign metastasizing struma, 221

cancer, 366

carcinosarcoma, 368

discrete adenoma, enucleation, 366

distant metastasis, 367

extracapsular finger dissection, 368

Graham, 220, 366

intrathoracic extension, 369

intratracheal catheter, 367

invasion of lymphatics, 365

Labey, 367

lavage with sterile water, 368

malignant degeneration, 365

mediastinal extension of malignant tissue, 368

oxygenation during operation, 367

papillary cystadenomas, 223

radical neck dissection, 367

roentgenotherapy, postoperative, 369

small cell carcinoma, 368

submandibular extensions, excision 367

subtotal thyroidectomy, 367

total hemithyroidectomy, 367

tumors of papillary, 368

Ward, 220, 367-369

Malignant degeneration, 365

Malignant growths, 51

Malignant lesions of thyroid in childhood, 218

Kennedy, 218

Pemberton, 218

Malignant metastases, 33

Malignant or progressive exophthalmos, 411, 413

Malignant tumors, 12-13, 53, 214-220

age incidence, 217

benign tumors, 215

carcinomas, 214

Clute and Warren, 215

DeQuersin 217

Eberts, 217

epithelial in origin, 12

Graham 214

Haagenesen 215

histopathological classification, 214

incidence and geographical region, 217

incidence of different histopathological types, 219

Kocher, 217

Labey, Hare, and Warren, 217

Langhans struma, 216

malignant lesions of thyroid in childhood, 218

metastatic lesions, 12

mixed tumors, 214

papillary tumors, 216

Pemberton, 217-219

Portmann, 219-220

pre-existing adenoma, 12

rapid metastasis, 12

sarcoma, 214

sex incidence, 218

- Speese and Brown*, 216
 toxic diffuse goiter, 12
Ward, 216 218
Warren, 215
Watson and Pool, 218 219
Wegelin, 217
Wells and Huguenin, 217 218
Mall, F P, 27, 33, 63
Mallet, L, 199
Malpighi, 15
Man, E B, 128, 132, 136, 139, 147, 312, 327
Mann, W, 195, 199
Mannaberg, J, 319, 328
Mansfield, Robert, x
Maresch, R, 63
 Marginal sinus, 54
Marie, P, 19, 24
Marine, D, 3, 18, 20, 24, 27, 67, 90, 104, 111 112, 118, 122, 163 164 195, 270, 278, 283, 290, 298
Marinelli, L D, 164
 Marked exophthalmos and progressive exophthalmos following thyroidectomy, 410
Marshall, C F, 39, 63
Maruno, Y, 137, 139, 147
Mask, 342
 Masked hyperthyroidism, 294, 302
Masson and Mueller, 57
Mason, V A, 63
Mastin, E V, 70 73, 90
Mauer, F, 33, 63
Maurice, 276, 283
Mayo, C W, 399
 Mayo Clinic, 409
McArthur, J W, 164
McCarrison, R, 90, 268, 273, 289 290, 298
McCarty, W C, 239
McClendon, J F, 109, 112, 118
McClintock J C, 39, 61, 247, 264, 271 272, 282
McClure, R D, 119
McCormick, E K, 328
McCullagh, D R, 130, 147
McCullagh, E P, 147, 264, 266, 272
McGavack, T H, 164
McGrath, E J, 264, 273
McIler, M A, 138, 147, 384
McKay, E A, 132, 148
McKnight, R B, 253, 272
McMillan, R M, 398
McSwain, B, 247, 264, 267, 269, 272
Means, J H, 14, 43, 103, 118, 123 124, 127, 145, 147, 164 165, 198 200, 306, 312, 328, 411-413, 416
 Medial lymphatics, 74
 Median aberrant thyroid tumor, 53
 Median anlage, 52
 Median primordium, 41, 50
 Mediastinal extension of malignant tissue, 368
 Mediastinum, 45, 69
 Medications, 13
 radioactive iodine 13
 thiouracil, 13
 thiourea, 13
Meeker, 243
 Mental confusion, 296
 Metabolic anomalies, 19
 Metabolism, vii, 4
 Metabolism of radio iodine as affected by high and low temperatures, 177
 exposure of animals to heat, 177
 histological study, 177
 Leblond, 177
 thyroid tissue of animals exposed to cold, 177
 Metabolism regulation, 19
 Metastases, ix, 53 54
 to the cervical lymph nodes, 53 54
 from primary tumor, 55
 Metastatic tumor, 225
 Metastasizing struma, 219
Metcoff, J, 91
 Metycaine, 334
Metzger, N, 163, 195
 Middle cervical fascia, 69
 Migration of argyrophil, 86
 Migratory thyroiditis, 158
Miller, J M, 399
Miller, R H, 63
Miller, W H, 199
Missal S, 250, 271
 Mitochondria, 81

- Mitosis of epithelial cells, 213
 Mixed tumors, 214
Moebius, P J, 19, 24
 Mochius sign, 277
 Mono cystic tumor of thyroid, 211
Montgomery, M L, 50-51, 63
Moore, E C, 264, 273
Moore F D, 147, 156 157, 160, 165
Moore M C, 119
Moore, S W, 247, 264, 267, 269, 272
Moorhead, T G, 404, 416
Mora, J M, 292, 295, 299
 Morbid appetite, 19
Morgan, E S, 404, 415
Morgen 57
Moritz A F, 63
 Morphine, 296, 332, 395
 Morphine sulfate, 332
Morris, A E, 402, 417
 Mortality rate following thyroidectomy
 for toxic goiter, 311
Morton M E, 125 126, 176, 199 200
Moseley, B, 15, 24
Moseley H W, 119
Mossman H W, 62
 Movable discrete adenoma, 212
Müller, F, 19, 24
Müller, W, 27, 63
 Müller's muscle, 277
 Multiple labeling, 187
Murphy, A J, 196
Murray, G R, 18, 24
Murray, N A, 58, 63, 92
 Muscular response to thyroid hormone,
 101
 degenerative changes in muscles,
 101
 hypotonicity, 101
 interstitial edema of the fibers, 101
 myasthenia, 101
 myxedematous infiltration of the car-
 diac musculature, 101
Mussey R D, 103, 119
 Myasthenia, 101
 Myocardial changes, 8
 Myocardial disease, 326
 Myocardial injury, 324
 Myosarcoma, 220
 Myxedema, 16 20, 107, 191, 244, 275,
 355
 Myxedematous infiltration of the car-
 dia musculature, 101
- ## N
- Nafe, C A*, 400-401, 416
Naffziger, H C, 412, 416
 Nausea and vomiting, 384
 Necrosis of the liver, 384
 Nephritic hypertension, 319
 Neoplasia, 36
 Nerve supply, 75
 Berlin and Labey 75
 Fowler and Hanson, 75
 Higgins 75
 neurofibrillae, 75
 perifollicular plexuses, 75
 perivascular plexuses, 75
 recurrent laryngeal nerve, 75
 Simon, 75
 tracheoesophageal groove, 75
 Weeks and Hinton, 76
 Ziegelman 75-76
 Nerves to the parathyroids, 69
 Nervous irritability, 311
 Neurocirculatory asthenia, 303 304
 Neurofibrillae, 75
Neucomer H S, 165
Neuman E V, 21, 24, 165
Nicholson, M J, 334 336, 339
 Nitrous oxide and oxygen, 47, 329
 330, 334
Nizzi-Nutt, G, 88, 286 287, 298
 Nodular goiter, 11, 209, 214, 241, 311
 enucleation of the nodules, 11
 fibrillation, 11
 myocardial damage, 11
 Nodular non toxic goiter, 109-110
 non toxic adenoma, 109
 carcinoma, 110
 fetal rests, 109
 Nodular thyroid, 123
 Nodular toxic goiter, 209, 380
 Nodules in contralateral lobe, 363
 Nodules of mixed type, 87
 Nodules in an otherwise 'normal'
 gland, 86-87

- Clerc*, 87
 colloid nodules, 87
 degenerate nodules, 87
Hellwig, 87
 histologic structure, 87
 hyaline stroma, 87
 incidence, 87
 infancy, 86
 interlobular stroma, 87
Jaffe, 87
 nodules of mixed type, 87
Nolan, 87
 parenchymatous (fetal) nodules 87
 puberty, 86
Rice, 86 87
Nolan, L. E., 67, 87, 90, 287, 299
 Non differential masses or fetal follicles, 35
 Non toxic diffuse colloid goiter, 173
 Non toxic diffuse goiter, 10 11
 acini, 10
 alveoli, 10
 bosselations 10
 clinical manifestations, 10
 colloid 10
 dessicated thyroid, 10
 hyperplasia, 11
 iodine, 10
 symmetrical enlargement of the thyroid, 10
 thyroid extract, 10
 Non toxic nodular goiter, 10, 213
Nora, E. D., 399
Nordland, M., 90
Norris, E. H., 34, 63, 84, 90
Norris, H., 16, 24
- O
- Ocular signs, 276
Oderfeld and Steinhaus 55
Oehme, C., 118
Olesen, R., 112, 114, 119
 Omohyoid, 68, 70
 Oophorectomy, 57
 Operability, measures of treatment and prognosis, 231-238
 alveolar adenocarcinomas, 234
 anaplastic tumor, 234
 bilateral infiltrating carcinomas, 235
 Broders 233
 discrete adenoma, 232
 Hare, 234
 Hertzler 235
 Labey Hare and Warren 236
 operative mortality, 236
 papillary adenocarcinomas 234
 Pemberton, 233 237
 Pemberton and Loxelace 236
 Pool 236
 Portmann 233 236 237
 results of operation 236
 Watson and Pool 237
 Welsh and Huguenin 237
 Operative considerations 340-381
 amount of gland to remove 355
 bilateral thyroidectomy technique, 343
 carcinoma 342
 cysts 347
 discrete adenoma 342 360 365
 errors on operating table 358
 intrathoracic goiter 342 368 372
 lateral aberrant thyroid bodies, 342
 lateral aberrant thyroid tissue 374
 ligation of thyroid arteries, 375 380
 malignant adenomas 365 368
 mortality 340
 sinuses 342
 thyroglossal rests 372
 thyroglossal tumors, 342
 unilateral thyroidectomy, 359 360
 Operative load on patient, 359
 Operative mortality, 236
 Operative technique, 21
 Optimal diet, 300
Ord W. M., 16 17, 24
 Origin of tremor, 280
 Langley 280
 sympathomimetic toxin, 280
 tonus in voluntary muscles, 280
Orr, J. B., 119
Osuald 93
 Ovarian struma, 184
 Ovarian teratoma, 56
 Overdigitalization, 387
 Overfunction, 15

Otternar, R, 306, 327
 Oversedation, 391
 Oxidative processes, 20
 Oxygen deficiency, effect on myocardium and adrenal medulla, 393
 Oxygen therapy, 382
 Oxygenation during operation, 367

P

Page I H 290, 299
Palmer, M W', 155, 165
Palmer, W' W' 146, 196, 198
Palmieri, M I 306, 327
 Palpable symmetrical enlargement, 8
 Papillary adenocarcinomas, 217, 223-224, 234 235
 anaplastic inversion, 224
 acute, sparse, 224
 carcinoma of thyroid, part alveolar, part papilliferous, 225
 carcinoma of thyroid, part diffuse, part papilliferous, 226
 intracystic papilliferous adenoma of thyroid, 223
 metastatic tumor, 225
 papilliferous carcinoma of thyroid, 224
 Papillary adenomas, 202
 Papillary carcinoma of the thyroid, 54, 216 219, 224
 Papillary cystadenomas 52, 225
 Papillary cystic thyroid tissue, 54
 Papillary fetal adenoma, 60
 Papillary hyperplasia, 204 205, 207
 Papillary infolding, 203, 210, 213
 Papillary nature, 51
 Papillomatous tumors, 51 52, 216
 Paracelsus, 16, 24
 Paralysis of recurrent laryngeal nerve, 212
 Parathyroids, 17
 deficiency, 396
 edema, 398
 extract, 396
 nervous phenomena, 17
 nodules, 50
 removed, 17

tetany, 395-398
 blood calcium, 396
 calcium chloride solution, intra venous administration, 396
 calcium lactate, 397
 carpopedal spasm, 396
 cause, 395
 Chvostek's sign, 397
 desiccated thyroid, 398
 dihydratichysterol, 397
 edema of parathyroids, 398
 epileptiform convulsions, 396
 Erb's sign, 397
 hypoparathyroidism, 396 398
 hypothyroidism, 398
 parathyroid extract, 396
 serum calcium, 396
 spasm of glottis or diaphragm, 396
Swinton, 395
 tetany, temporary, 398
 Trousseau's sign, 397
 Paratracheal and deep cervical glands, 75
 Paratracheal and pretracheal glands, 75
 Parenchyma, 2, 6
 Parenchymal arteries, 70
 Parenchymatous (fetal) nodules, 87
Parkhill, E M 213, 239
Parmley C C 212, 247, 254, 272
Parry, C H, 18 19, 24
Paschke, K E 81, 90
Paschke, M V 165
 Pathological aspects 22
 Pathological findings 13
 Pathological physiology, 18
 Pathology, ix, 201-236
 adenocarcinoma of thyroid, 226-229
 adenomatous goiter, 207
 carcinoma sarcoma, 229
 diffuse non toxic goiter, 201
 diffuse toxic goiter, 202
 malignant adenomas, 220 223
 malignant tumors, 214
 operability, measure of treatment and prognosis, 231 238
 papillary adenocarcinoma, 223 225

- relation of adenomas to malignancy 210
- sarcoma, 230 231
- significance of staining properties of colloid, 207
- simple colloid goiter 201
- Peacock W* 147, 198, 200, 328
- Pearse, I H*, 65, 264 265, 273
- Pedersen, S*, 392, 399
- Pemberton, J de J*, 54, 58 62 63, 90, 217 219, 227-228 231 233 239 399, 404, 416
- Penicillin, 308
- Pentobarbital sodium 332
- Pentothal sodium, 336
- Peptide linkage, 94
- Perazzo*, 392, 399
- Perforating tumor of the skull 55
- Periacinar capillaries 70 73
- Pericardium, 68
- Perichondrium separated from arytenoid, 390
- Perifollicular plexuses, 75
- Perifollicular septa, 75
- Perithyroiditis, 13
- Perivascular plexuses, 75
- Perkin, H J*, 22, 131 133, 137 147, 415
- Pearlman, I*, 199 200
- Persistent thyroglossal tract, 41
- Peters, J P*, 132, 139 146
- Pharynx, 48, 69
- Phemister D B* 404, 416
- Phenolic groups of diiodotyrosine, 106
- Philippines, 20
- Phillips, F J*, 145
- Phosphorus metabolism, 20, 101, 306
- Physiological aspects, 92
- Physiological principles, vii
- Physiology of the thyroid gland 92-116
 - acini, 92
 - Addisonian crisis 102
 - Algire*, 92
 - Althausen and Stockholm* 98
 - Baumann*, 93
 - calorigenic action, 94
 - of thyroxine, 102
 - cerebral cortical alpha, 98
 - chemical nature of thyroid hormone 92
 - congenital athyreosis 95
 - cretinoid syndrome, 92
 - cretinism 95
 - depletion of hepatic glycogen 98
 - desoxycorticosterone 102
 - dextrose tolerance, 98
 - diabetes mellitus, 98
 - diiodotyrosine 93 94
 - dwarfism 95
 - effect on circulatory system 99
 - effect on serum cholesterol, 99
 - effect on nervous system, 98
 - enzymic digestion 92
 - epinephrine, 102
 - epiphyseal cartilage, 95
 - exophthalmic goiter 98
 - follicle lumen 92
 - Goetsch test, 102
 - growth of nails and hair 96
 - Gull* 92
 - Harington and Barger* 93
 - Harington and Salter* 94
 - hematopoiesis and the thyroid 99
 - Hutchison and Osuuld* 93
 - hyperfunction, 110
 - hyperplastic thyroid 93
 - hyperthyroidism in pregnancy and lactation, 111
 - hypertrophy of the adrenal cortex 102
 - hypophysectomy 102
 - hypofunction, 106
 - hypofunction of the adrenal medulla, 102
 - inanition, 97
 - influence on carbohydrate metabolism, 98
 - iodine and thyroid physiology 105
 - Joll* 9, 36, 97
 - iodothyroglobulin, 93
 - juvenile myxedema, 95
 - Kendall* 93
 - Lerman* 99
 - MacKenzie and Fox* 92
 - Magnus Ley*, 93

- Murray* 92
 muscular response to thyroid hormone 101
 nodular non toxic goiter, 109
 oxidative reactions, 95
 peptide linkage, 91
 pituitary dysfunction 102
 primary hypothyroidism, 106
 protein fractions, 93
 proteolytic enzyme activity, 92
Randall Harington 93
 rat 92
 regional influences 111
 relation to the adrenal cortex, 102
 relation to adrenal medulla 102
 relation to menstrual disturbances, 103
 relation to sterility and abortion, 102
Reterdin and Kocker 92
 salamander, 92
Salter and Lerman 94
 secondary hypothyroidism 109
 secretory activity, 92
 sexual development, 95
 sheep, 92
 simple goiter, 109
Sternheimer 98
 substances having calorogenic action, 105 106
 tarsal bones, 97
 thyroglobulin, 92
 thyroid hormone 100
 and metabolism of inorganic salts, 100
 thyroxin polypeptide, 91
 total thyroidectomy results, 102
 water metabolism, 100
Williams and De Roberts, 92
Zondek 95
Pierson P H, 185 186, 200
 Pituitarectomy, 102
 Pituitary, 20
 dysfunction, 102
 thyrotropic hormone, 21
 Placement of cutaneous incision, 388
Plant A 63
 Plasma cells, 252
 Platysma, 68
Pliny the Elder 14
Plummer H S 20 21, 122, 142, 144, 165, 293 309, 318, 329, 375 381
 Pneumonia 213, 296
 Polynuclear cells, 245
 Polynuclear infiltration, 246
Pool E H 356, 358, 381
Pool J L, 218 219, 232, 236, 240
 Poor risk patients
 elderly patient, toxicity often masked, 316
 patient with cardiac condition, 316
 unilateral thyroidectomy, 316
Popoff A H 90
Poppen 112
Porta 35
Portmann U V 210 219 220, 226 227, 233, 236, 240
 Possible postoperative complications, 384-390
 auricular fibrillation and flutter, 387
 capillary ooze, 385
 causes of laryngeal or tracheal obstruction, 389
Clute, 388
 collection of mucus, 387
 congestive heart failure, 386
 control of bleeding, 385
 digitalization preoperative, 387
 elevation of temperature, 316
 extension of infection, 386
 flaxseed poultices 386
 hematoma, 385
 hemorrhage, 385
 hepatic difficulties, 386
Hoover 389
 incision along posterior border of lateral cartilage and inferior cornu, 389
 infection, 385
 jaundice, 386
King 389
 nausea and vomiting 384
 overdigitalization, 387
 perichondrium separated from arytenoid, 390
 placement of cutaneous incision, 388
 potential thyrocardiacs 386

- recurrent laryngeal nerves injury to, 387
- slow bleeding from small vessels 385
- thyrocardiacs, 386
- thyroid crisis, 390
- Woodman D* 388 391
- Postero lateral border of the sternothyroid 68
- Posteromedial part, 68
- Postoperative administration of iodine 10
- Postoperative care 382-399
 - care in immediate postoperative period, 382 384
 - complications, 382
 - parathyroid tetany, 395 398
 - possible postoperative complications 384 390
 - postoperative vigil 382
- Postoperative hypothyroid symptoms, 17
- Postoperative hypothyroidism 400 401
 - blood cholesterol 401
 - frequency of occurrence of, 401
 - incidence, 400-401
 - Nafe*, 400-401
 - recurrent or persistent hyperthyroidism, 401 409
 - significant factors 401
 - therapeutic test, 401
- Postoperative sequelae, 400-417
 - disturbance of ocular muscles 413
 - importance of period examinations 414
 - postoperative hyperthyroidism, 400 401
 - rehabilitation, 414
- Postoperative hypothyroidism 314
- Postoperative reaction, 310
- Postoperative sedation, 333
- Postoperative thyroid shock, 324
- Postoperative treatment, 8
- Postoperative vigil, 382
- Potassium salts, 100
- Potential hyperfunction, 13
 - iodine medication 13
 - non toxic diffuse goiter, 13
 - non toxic nodular goiter, 13
 - surgery, 13
 - thyroid medication, 13
- Potential thyrocardiacs 386
- Precapillary arteriole showing sclerosis, 257
- Preglandular muscles 59
- Prelaryngeal glandules 74
- Premedication of children with hyperthyroidism 338
- Preoperative crisis, 391
- Preoperative considerations 300 328
 - adequate medication 300
 - adequate rest 300
 - administration of desiccated thyroid, 310
 - Barker and Wood* 311
 - blood pressure, 318 327
 - in myxedema 321
 - Cole* 311
 - DeCourcy* 310
 - differential diagnosis, 303 304
 - effects of goitrogenic drugs 312
 - Fitzgerald*, 311
 - glycosuria, 320
 - goiter heart 322 326
 - hypertension, 320
 - iodine with thio drug 312 314
 - Lugol's solution 310
 - mobility or fixation of thyroid gland, 301
 - optimal diet, 300
 - poor risk patients unilateral thyroidectomy, 316
 - preoperative treatment, 304 315
 - prerequisite for bilateral thyroidectomy, 315 316
 - prerequisites for thyroidectomy, 315
 - propylthiouracil, 300
 - psychic factors, 300
 - relation of blood pressure to basal metabolic rate, 319
 - roentgenotherapy, 317
 - serum iodine, 311
 - study of patient, 301, 303
 - thiouracil, 300
 - thio drug medication 310

- thio drug therapy, 314
 thyroid crisis, 311
 thyroid storm, 311
 transient hyperglycemia from emotional perturbation 321
 Preoperative diet 296
 Preoperative management, ix
 Preoperative treatment, 307-315
 aim, 301
 B vitamins 8, 306
 calories per day 306
 daily allowance of protein, 306
 danger of excess fat, 306
 diet, 306
 Linman 306
 informal psychotherapy, 305
 intravenous amino acid alimentation, 306
 liver deaths 306
 rest, 305
 thiamin requirements 306
 vitamin D 306 307
 Williams 306
 Prerequisites for bilateral thyroidectomy, 315 316
 basal metabolic rate, 316
 in cardiac complications, 315
 complicating disorders, 316
 gain in weight 315
 general physical and mental condition, 315
 resting pulse rate, 316
 Prerequisites for thyroidectomy, 315
 timing 315
 Presence of palpable thyroid tissue after operation, 10-1
 Pressure on cervical sympathetic nerves, 282
Preston, J W 102, 404, 415 416
 Pretracheal fascia, 68
 Prevertebral fascia, 69
 Primary cancer, 12
 clinical recognition, 12
 distant metastasis, 12
 nodular goiter, 12
 prevention of recurrence, 12
 total removal, 12
 x ray treatment, 12
 Primary hyperthyroidism, 201
 Primary hypothyroidism, 106
 Primary osteogenic type, 219
 Primary resections, 358
 Primary squamous epithelioma, 219
 Primary toxicosis, 277
 Primary tumor, 52
 Primitive vertebrate, 29
 ammocoetes 29
 amphioxus, 29
 cyclostome, 29
 endostyle, 29
 Imprey Petromyzon, 29
 metamorphosis, 29
 Problems of a second thyroidectomy, 109
 Procaine, 331
 Procaine hydrochloride, 331
 Profuse peripheral anastomoses, 71
 Prolonged thio drug medication, 313
 Propylthiouracil, 123, 161-163, 300, 312, 340, 358, 408
 for thyrotoxicosis, 161
 Astwood and Vanderlaan, 161
 163
 outstanding observation, 162
 side effects 162
Prosser 9, 15, 21
 Protein bound iodine, 21, 132
 Proteolytic enzyme activity, 92
 Protrusion of the eyes, 410
 Province, 132
 Pseudocapsule, 207
 Pseudogiant cells, 252, 259
 Pseudogranulomata, 259
 Psychic factors, 300
 Psychotherapy, 21
 Puberty, 4
 Pulmonary tuberculosis, 303
 Pulse rate during anesthesia, 359
Puppel I D 117, 172 173, 306, 328
 Pure ovarian strumas, 59
Purjes H D, 89, 149
 Pyogenic infections, 213
 Pyramidal process (lobe), 38-40
 Beilby 39
 Berlin, 39
 cartilage and fascia round the thy-

roid strand, 39
 fifth week of fetal life, 39
Grüber, 39
 hyoid anlage, 38
 levator glandular thyroidea, 39
Joll, 39
Marshall, 39
McClintock, 39
 periosteum of the hyoid, 38
 thyrohyoid, 39
 thyroid anlage, 38
 thyroid epithelium outside the gland, 39

R

Raab, W., 393, 399
 Rabbits, 19
 Radical neck dissection, 367, 374
 Radioactive iodine, 21, 60, 125, 176
 Radioactive iodine therapy in hyperthyroidism, 186-191
Chapman and Evans, 187
 dosage, 188
 Geiger Muller counter, 187
 Graves disease, 191
Hamilton, 186
Hertz, 186 187
Hertz and Roberts, 187
 large doses administered to animals, 186
 multiple labeling, 187
 preliminary studies, 186
 quantity in gland after intravenous injection, 186
 therapeutic doses, 187
 tracer doses, 187
 as tracer in study of thyroid physiology, 186
 Radioactive isotopes of iodine, 166-190
 activity of diffusely distributed iodine, 168
 artificially produced, 166
 atomic weight, 166
 biochemical investigations, 169
 element 85, aka iodine, 195
 excretion, 168
Fermi, 166

Geiger Muller counter, 166
Hamilton, 168 169
Hamilton and Soley, 168
Hertz Roberts and Evans, 167 168
 iodine metabolism in Graves disease, 177
 metabolism as affected by high and low temperatures, 177
 production, 167
 results obtained with radioactive iodine (130 and 131) in Graves disease, 190
 side effects and possible delayed reactions, 193
 standard vacuum tube amplifier, 167
 thyroid carcinoma, 166
 toxic reactions, 167
 as tracer for differential diagnosis in primary carcinoma of trachea, 186
 tracer dose, 166
 use in therapy of diffuse toxic goiter, 166
 Radioautograph technique, 60
 Radio—(radio iodine) iodine, 184
 180-182
 in childhood hypothyroidism, 180
 accumulation in the thyroid, 180
 dosage, 181
 Geiger Müller counter, 180
 in goitrous cretins, 181
Hamilton, 180 181
Hamilton Soley, Reilly and Eulborn, 180
Hertz, 181
Hertz and Roberts, 180 181
 in hypothyroidism, 181
 in hypothyroidism but without goiters, 181
 inability to absorb, 180
 retention, 181
 thyroid tissue of adults with myxedema, 182
 Radiotherapy, 183
 Radiothyroxin, 126
Rakoff, A. E., 90, 165
Ramsay, A. J., 90
 Ramus communicans, 70
Randall, S. S., 93, 117, 197

- Ransom, H K* 391, 399
 Rapidly growing carcinoma, 60
 from embryonal epithelium, 60
Rapport D 106, 117
Rauson, R W, 80, 90, 121 123, 147,
 157, 161 163, 198 200, 312 313,
 328
Rea C 333, 337 339
 Recurrence, 26
 Recurrent hyperthyroidism, 135, 328
 Recurrent laryngeal nerve, 73
 injury to, 387
 Recurrent or persistent hyperthyroid
 ism, 401-409
 administration of desiccated thyroid,
 105
 administration of iodine, 408
Cattell and Morgan 401
 causes 102
DeCourcy 102
DeCourcy Clinic, 105
 desiccated thyroid 105, 108
Dimmore and Crile 409
 exophthalmos, 109
Haines and Pemberton 101
 incidence, 102 403
 increased prominence of the eyes
 following medical and surgical
 treatment, 109
Moorhead 101
Phemiston and Delaney, 101
 presence of palpable thyroid tissue
 after operation, 401
Preston and Thompson, 102, 401
 prevention, 101
 problems of a second thyroidectomy,
 109
 propylthiouracil, 408
Reinhardt, 101
Rienhoff, 107
 roentgenotherapy, 408
 this drug, 108
Thompson Morris, and Thompson,
 102
 treatment, 108
 Recurrent thyrotoxicosis, 10
Regan, J F, 307, 328
Reggiani E 287, 298
 Regional anesthesia, 333
 Regional influences, 111-116
 Baumann, 111
 Chatin, 111
 Comdet, 111
 Courtois, 111
 Curtis, 116
 Daly, Sir Humphry 111
 Gay Lussac 111
 Iodized Salt Committee, 113
 Marine 111 112
 McClendon 112
 Olesen 112, 111
 Regional teratomas, 59
 Rehabilitation, 414-415
 Berlin and Gargill, 415
 DeCourcy, 414
 Pemberton, 414
 Preston and Thompson 415
Reilly, W A 180, 197
Reinhardt, W O 199, 401, 416
 Relation of adenomas to malignancy,
 210 214
 Broders and Parkhill 213
 cancer among patients with nodular
 goiter, 212
 chemotherapy of Graves disease,
 213
 embryonal or fetal adenomas, 212
 epithelial malignant tumors, 210
 Hinton and Lord, 210, 214
 fixation 212
 involved Graves type thyroid, 212
 Labey 212
 movable discrete adenoma, 212
 non toxic nodular goiter, 213
 paralysis of recurrent laryngeal ner-
 ve, 212
 Portmann, 210
 thyroid cancers, 210
 Ward, 210
 Warren, 210
 Relation to the adrenal cortex, 102
 Relation to adrenal medulla, 102
 Relation to the parathyroids, 69
 Relation of thyroid hormone to food
 factors, 96-98
 high protein diets, 96

- in hyperthyroidism, 98
- in anition, 97
- Leutz*, 97
- unbalanced diets, 98
- vitamin A, 97
- vitamin C, 97
- vitamin deficiencies, 96
- Relation to menstrual disturbances, 103
 - amenorrhea, 103
 - menorrhagia, 103
 - Mussey and Haines*, 103
 - oligomenorrhea, 103
- Relation to sterility and abortion, 102-103
 - basal metabolism, 103
 - habitual abortion, 103
 - Hertoghe*, 103
 - in hyperthyroidism, 102
 - Means*, 103
 - spermatogenesis, 103
- Relations with cervical fascia and muscles, 68-69
 - anastomosing vessels, 69
 - anastomotic branch, 68
 - anterior juglar veins, 68
 - attachment of gland to larynx, 69
 - blood supply of the parathyroid bodies, 69
 - carotid sheath, 68
 - cervical fascia, 68 69
 - contraction of the stylohyoid muscle, 68
 - cricoid cartilage, 68 69
 - cricothyroid muscles, 68
 - deglutition, 68
 - esophagus, 69
 - external capsule, 68
 - inferior constrictor, 68
 - inferior parathyroid body, 69
 - inferior thyroid artery, 69
 - inferior thyroid veins, 68
 - insertion of sternothyroid into oblique line of lamina, 68
 - internal capsule, 68
 - lateral lobe, 69
 - longus capitis, 68
 - lymphatic systems of the thyroids and parathyroids, 69
 - mediastinum 69
 - middle cervical fascia, 69
 - nerves to the parathyroids 69
 - omohyoid, 68
 - pericardium 68
 - pharynx, 69
 - platysma, 68
 - postero lateral border of the sternothyroid, 68
 - posteromedial part 68
 - preglandular muscles 69
 - pretracheal fascia, 68
 - prevertebral fascia 69
 - relation to the parathyroids, 69
 - scattered island of parathyroid tissue, 69
 - sternocleidomastoid 68
 - sternohypoid, 68
 - sternothyroid muscle 68
 - superficial fascia, 68
 - superior thyroid arteries 68
 - superior parathyroid bodies 69
- Relative deficiency 104
- Remak R* 27, 64
- Remington R E* 67 91
- Renal threshold for sugar 320
- Renon, J M* 271, 273
- Replacement of glandular structures by lymphoid tissue, 247
- Report on myxedema, 23
- Reptiles, 29
- Response to iodine, 110
- Rest, 305
- Results obtained with radioactive iodine (130 and 131) in Graves disease, 190 192
 - Chapman and Evans*, 192
 - Hertz and Roberts*, 190 192
 - important clinical considerations, 191
 - insuring maximum concentration of radioactive isotopes by thyroid, 190
 - in large, involutional goiters, 192
 - myxedema, 191
 - in ophthalmopathic groups of hyperthyroidism, 192
 - potassium iodide, 190

- radioactive iodine therapy in Graves disease 191
- roentgen therapy 192
- sodium iodide 190
- toxic reactions 192
- total activity administered 190
- Results of operation 236
- Retardation of bone formation 101
- Retention cysts 41
- Reticulum cell lymphosarcoma 230
- Retrosternal goiter, 12
 - removal of, 371
- Reteno W S* 312, 329
- Reterdin J L* 17 24 92
- Rhabdomyosarcoma 220
- Rice C O* 66 67, 77 78 95 87 287 299
- Richardson L P* 11
- Riddell C B* 117
- Riedel B M C L* 55 217 265 272
- Riedel's disease 12
- Riedel's struma 11 13 212 247 263, 266-270
 - acinar epithelium 252
 - actinomyces 253
 - acute nonsuppurating thyroiditis 261
 - administration of iodine in nodular goiter 262
 - avascularity of gland 251
 - basal metabolic rate 218
 - benign granuloma 253
 - Bothe* 217, 251
 - Boyden Collier and Bugher* 262
 - carcinoma 250
 - causation of struma fibrosa 263
 - chemical perithyroiditis 262
 - clinical features 218
 - Clute*, 247
 - connective tissue infiltration 219
 - Cross* 217
 - DeCourcy* 217 251
 - DeCourcy Clinic* 250 255
 - DeQuersain* 217, 252
 - DeQuersain and Giordanengo* 217 261
 - differential diagnosis 250
 - differentiation from diffuse toxic goiter 250
 - dysphagia 249
 - edema 219
 - epithelial cells 252
 - evidence of hypofunction, 218
 - extraglandular fibrosis 250
 - Ewing* 253 264 265
 - fibrosis 259
 - fibrous growth 11
 - fibrous tissue 11
 - fibrous whorls 251
 - Fox and Mussil* 250
 - Germane* 259 260
 - giant cell variant of struma fibrosa 250
 - Goldblatt* 251 255
 - Goetsch* 252
 - Gratam* 217 253
 - gross appearance 251
 - Hurry* 217 253 255
 - Hashimoto* 247
 - Hashimoto's disease 250
 - Hertzer* 217 219 255
 - histopathologic features 251
 - hyalinization of the stroma 257
 - hypertrophy of media 256
 - involvement of laryngeal nerve 250
 - iron hardness 250
 - Joll* 217
 - Lee* 250
 - ligneous or woody thyroiditis 217 252
 - Lugol's solution 256 262
 - lymphocytes 252
 - McClintock and Wright* 217
 - McKnight* 253
 - McSwain and Moore* 247
 - microscopic examination 251
 - Parnley and Hellwig* 217 251
 - partial occlusion of renal blood vessels 111 251
 - pathologic features 251
 - pathologic process 262
 - plasma cells 252
 - perithyroiditis 11
 - precapillary arteriole showing sclerosis 257

- pseudogiant cells, 252, 259
 pseudogranulomata, 259
 replacement of glandular structures
 by lymphoid tissue, 247
 result of previous perithyroiditis,
 247
Riedel, 247
 role of perithyroiditis, 254
Schilling, 247-248, 250, 252, 254,
 261
 sclerosed arterioles and obliteration
 of thyroid acini by fibrous tissue,
 258
 secondary fibrosis, 255
 streptococci, 253
 struma fibrosa, 261
 struma lymphomatosa, 247, 251, 253
 subtotal thyroidectomy, 11
 syphilis, 252
 theories of etiology, 252
 thickening of intima and media of
 blood vessels, 254
 tracheal obstruction, 249
 true giant cells, 252
 tuberculosis, 252
 wandering monocytes, 252
Womack, 247-248, 254
Zelle, 254, 262
Rienhoff, W F, Jr, 64, 70, 73 90,
 407-416
Riggs, D S, 128 129, 132, 136, 147
 Ringer's solution, 170
Roberts, W M, 61
Roberts, A, 67, 177, 179 181, 187
 193, 197-198
Robertson, J D, 146
Rodriguez, 132
 Roentgen irradiation, ix
 Roentgen therapy, 192, 297
 Roentgenotherapy, 317, 408
 Cole, 317
 postoperative, 368
 Thompson and Thompson, 317
 x ray treatment, 317
Roger, 241
Roger of Palermo, 16
Rogers, W M, 33 34, 64
Rogouitsch, 102
Rolleston, H D, 16
Rose, 149
Rosellini, L J, 158, 164
Rosenkrantz, J A, 284, 289 290, 297
Rosenthal, A A, 62
Rossiter, L J, 238
Rothenberg M S, 90
Roentstine, E A, 338 339
Ruedemann, A D, 411 413, 416
Rumph, P, 64
 Rupture of the duct, 31

S

 Saline solution, 333
 salivary gland acini, 42
Salley, D J, 199
Salter W T, 94, 106, 117 124, 132
 133, 147, 177, 179, 189 197, 200
Saltzman 132
Sandiford I 117, 289 297
Sandiford K 117
Sappington, A M 132, 148
 Sarcoma, 214, 219, 230 231
 combined surgical and roentgen
 treatment, 230
 fibrosarcoma of thyroid, 230
 lymphosarcoma, 230
 Pernberton, 231
 Portmann, 231
 reticulum cell lymphosarcoma 230
 Scalenus anticus muscle, 71, 379
Scarcello N S 271, 273
Schachner H, 200
Scheffer, L, 139, 148
Schiff, J M, 17, 24, 42
 hypothyroid symptoms, 17
Schilling, J A, 247 248, 250, 252
 254, 261, 272
Schimmel, I 370, 381
Schittenhelm, A, 130, 148
Schlotthauer, C F, 90
Schrager, V L, 35, 51, 64
Schumakker, H B, Jr, 139, 146
Schummer, D, 164
 Scirrhus carcinoma, 220, 229
 Scirrhus growths, 216
 Sclerosed arterioles and obliteration of
 thyroid acini by fibrous tissue, 258

- Sclerosing carcinoma, 221
 Scopolamine, 332
 Scopolamine hydrobromide, 332
Scott 280
 Secondary fibrosis, 255
 Secondary hypothyroidism, 1, 109
 Addisonian crisis 109
 Addison's disease, 109
 anterior lobe of pituitary, 109
 desiccated thyroid, 4
 etiologic factors, 109
 hypophysis 109
 stimulation therapy, 1
 Secretory activity, 92
 Secretion antecedents, 82-83
 basal vacuolar substance, 83
 Bensley 82-83
 chromophobic vacuoles, 82
 colloid droplets, 82
 cytological precursors, 82
 DeRobertis 82
 discharge of intrafollicular colloid, 83
 Langendorff 82
 Thomas 83
 Thomas staining technique, 83
 transcellular release of colloid, 83
 Uhlenhuth, 83
 Sedation, 332-333, 383, 395
 atropine, 332
 dosage 332
 inhalation anesthesia, 333
 intravenous glucose solution, 333
 intravenous pentothal, 333
 morphine, 332
 morphine and scopolamine, 332
 morphine sulfate, 332
 pentobarbital sodium, 332
 Rea 333
 saline solution, 383
 scopolamine, 332
 scopolamine hydrobromide, 332
Seel H, 290, 299
Sendlin, S M, 164
 Senescence, 281
 Sensation of warmth, 18
 Septa primary lobules 76
Serrano, J A, 18, 22
 Serum calcium, 396
 Serum cholesterol, 129
 Serum iodine, 311
 level, 132
 Serum precipitable iodine 129
 normal concentration, 132
Serringhaus A E 90
Serringhaus, E L 399
 Sex incidence, 218
 Sexual development, 95
Sgalitzer, K E 64
Shapiro P F 64
Sharp, E A 165
 Sheep's thyroids, 15
Shneley, F L 331, 339
Sborr, 400
 Side effects and possible delayed reactions, 193-194
 cancer as result of irradiation, 193
 Chapman and Evans 193
 damage to cells of kidney, 194
 fibrosis of thyroid, 193
 Hertz and Roberts, 193
 hyperthyroidism treated with radioactive iodine, 193
 injury to spermatozoa or ova, 194
 Lawrence, 193
 ophthalmopathic groups of hyperthyroidism, 193
 Significance of blood iodine level, 129
 Significance of staining properties of colloids 207
 atrophic epithelium, 207
 basophilic colloid, 207
 cellular hyperplasia 207
 Hertzler, 207
 thick colloid, 207
 thin colloid, 207
 toxic goiter, 207
 Signs of von Graefe, Stellwag, and Mochius, 276-278
 levator palpebrae superioris, 277
 Mochius sign, 277
 Müller's muscle, 277
Silber, P G, 239
Smendinger, L A 139, 148
Simon M M, 75, 91

- Simple colloid goiter, 122, 201-202
 alveoli, 202
 anoxemia of cells, 202
 colloid retention, 202
 cuboidal epithelium, 202
 cystic degeneration, 202
 deposition of colloid, 201
 distention of acini, 202
 fibrosis and calcification, 202
 follicles, 202
 functional hyperplasia, 202
 intracrinous adenomas, 202
 intrathoracic goiter, 202
 papillary adenomas, 202
 prepuberty to late adolescence, 201
 vacuolization, 202
- Simple goiter, 109
 McClendon 109
- Sinuses, 342
- Sinusoids, 54
- Sisk, W N, 165
- Skin disorders, 19
- Slaughter, D P 238, 364, 381
- Sloan, L W, 196
- Slosse, J, 117
- Slow bleeding from small vessel, 385
- Small alveolar and large cell adenocarcinomas, 219
- Small cell carcinoma, 368
- Small round cell carcinoma, 227 228
- Smirnov, A E, 147
- Smith, L W, 63
- Smith, P E, 64
- Smith, R D, 91, 299
- Sodium iodide, 395
- Soley, M H, 168, 179 180, 182, 194, 197, 409, 416
- Soskin, S, 165, 200
- Spain, D M, 164
- Spasm of glottis or diaphragm, 396
- Speese, J, 216, 239
- Spermatogenesis, 103
- Spinal anesthesia, 337-338
 Bartels, Stuart, and Johnson, 337
 combination of intravenous pentothal and inhalation anesthesia, 337
 Crile, 337
 Knight, 337-338
 Rea, 337-338
 Trendelenburg position, 338
- Spindle cell carcinoma, 227 228
- Spindle and giant cell adenocarcinoma 219
- Splitting the sternum, 43
- Spontaneous myxedema, 108
- Sporadic cretinism, 17 20, 96 97
- Spring goiter, 42
- Spron, H, 64
- Squamous epithelium arising 41
- St John, R, 399
- Stalker, L K, 399
- Staphylococci, 243
- Starkey W F, 299
- Starr, P, 80, 90 91
- Steer, A E 72
- Stebbins, H D, 118
- Stein, H B, 91
- Stern, F, 130, 148
- Sternheimer, 98
- Sternocleidomastoid, 68
- Sternohypoid, 68
- Sternomastoid, 70 73
- Sternothyroid, 68
- Stevens, C D, 137, 148
- Stewart, J D, 52 53, 70, 91
- Stieda, L, 27, 32, 64
- Stockholm, 98
- Stone, R S, 199
- Strecksien, A 64
- Streptococci, 243
- Stroma, 241
- Struma fibrosa, 263
- Struma lymphomatosa, 159, 242 247, 251, 253, 265 267, 270
- Struma ovarii-ovarian goiter, 56-59
 benign tumors, 57
 cystic and solid ovarian tumors, 58
 dermoid cysts, 58
 Emge, 56 57
 folliculoma malignum ovarii, 56
 from embryonic rest, 59
 Frankl, 58
 functioning ovarian strumas, 58
 Gottschalk, 56
 growth characteristics, 57

- Gusberg and Danforth* 56, 58
hyperplastic strumal tumor, 58
hyperthyroidism, 57
macrofollicular, 58
Masson and Mueller, 57
microfollicular, 58
Morgen 57
Murray Dockett and Pemberton
58
oophorectomy, 57
ovarian teratoma 56
presence of aberrant thyroid tissue
56
pure ovarian strumas 59
regional teratomas 59
teratoma, 58
three fetal layers, 58
three germinal layers 58
thyroid rests 56
Trapl, 56
Strumitis, 212
Stuart C K 297 337, 339
Study Committee on Endemic Goiter of
the American Public Health Asso-
ciation, 20
Study of patient 301-303
blood cholesterol level, 302
blood count, 301
blood iodine determination 302
cardiac examination 301
compression or deviation of trachea
301
diabetes mellitus, 301
eye signs, 301
galactose tolerance test, 302
gastro-intestinal symptoms, 301
hippuric acid test, 302
history, 301
laryngeal examination 301
muscle weakness, 301
nervous manifestations 301
other laboratory determinations, 301
physical examination, 301
renal damage, 301
repeated basal metabolic readings
301
Thompson, 301
Subclavian, 71
Subclavian artery, 72
Subclavicular goiter, 42
Subcutaneous edema, 244
Submandibular extensions excision
367
Substances having calorogenic action
105-106
calorogenic potency, 105
Canzanelli and Rapport 106
Cohn, Salter and Ferry 106
diiodothyronine, 106
diiodotyrosine, 105 106
Lerman, 106
Harrington 106
Lerman and Salter 106
phenolic groups of diiodotyrosine
106
thyroglobulin 105
thyronine, 106
thyroxin 105
tyrosine 105 106
Substernal adenoma of thyroid 18
Substernal fetal adenoma of thyroid 18
Substernal goiter, 42, 345
Substitution therapy, 17 18
Subtotal thyroidectomy, 8 309, 353
364 367
S  e P 174, 198
Sulfonamides 21
Sulfonamide therapy, 308 383
Sullivan J, 88
Superficial fascia, 68
Superfluous embryonal thyroid epithe-
lium, 59
Superior belly, 70
Superior laryngeal nerve 70 314
Superior lateral artery 71
Superior mediastinal glands 75
Superior parathyroid bodies 69
Superior pole, 70
dissected free, 317
ligation, 318
Superior thyroid arteries 68
Suppurating cyst, 42
Suppuration, 12, 242
Suprathyroid, 50
Suprathyroid thyroid nodule 50
Surgery, 9

Surgical approach, vii
 Surgical aspects, 3, 22
 Surgical indications, vii
 Suture of sternothyroid muscle to pre
 tracheal fascia, 356
 Sweating, 19, 322
Sweeney, D. N., Jr., 165
Swinton, N. W., 396, 399
 Swiss endemic disease, 14
 Sympathomimetic amines, 393
 Sympathomimetic toxin, 280, 282
 Symptoms referable to thyroid, 281
 bruit over thyroid 281
 Symptoms in thyroid crisis, 391
 Synergistic agents, 155
 Bartels, 155
 Palmer, 155
 Systolic murmurs 323

T

Tachycardia, 19, 122, 278 279, 322
 amino acid injected, 278
 associated with subjective symptoms
 of sympathicotonia, 278
 Basedow's disease, 278 279
 Boas, 279
 cardiac goiters, 278
 Eppinger and Hess, 278
 Kendall, 278
 Marine and Lenhart 278
Talbot, 132
Tannheimer, J. F., 200
 Tarsorrhaphy, 412
 Tarsal bones, 97
Taurog, A., 126, 148, 174, 200
Taussig, A. E., 318, 328
Taylor, N. E., 119
 Teratomas, 29, 58
 Tetany, temporary, 398
 Theoretical possibility of carcinogene
 sis, 158
 adenomas, 158
 Bielschowsky, 158
 carcinoma in situ, 158
 hyperplastic thyroid neoplasms, 158
 2 acetaminofluorine, 158
 Therapeutics, vii
 thiouracil, vii

 thiourea, vii
 Therapeutic test, 303 304, 401
 Therapeutic use of radioactive iodine
 in Graves' disease, 179
 Therapy, ix
 Thiobarbital, 159
 Astwood, 159
 Bartels, 159
 diethyl thiobarbituric acid 159
 toxic reactions 159
 Thio drug, 312, 340 408
 medication, 310
 therapy, 314
 Thiouracil, 20 21, 150 300, 312, 340,
 358, 410
 in acute thyroiditis 158
 Hashimoto's struma 159
 King and Rosellini 158
 Lugol's solution, 159
 migratory thyroiditis 158
 struma lymphomatosa 159
 and hyperplastic thyroid gland of
 Graves' disease, 312
 in hyperthyroidism associated with
 functioning metastases of adenocar
 cinoma, 158
 Graves' disease, 158
 Letter, 158
 in metastases of adenocarcinoma of
 thyroid, 185
 mode of action, 313
 structural formula, 150
 6 isobutyl thiouracil, 160
 Williams, 160
 therapy, 154
 and thiourea in thyrotoxicosis, 127
 treatment, 125
 Thiouracil, propylthiouracil and re
 lated drugs in treatment of thyro
 toxicosis, 149-154
 antithyroid drugs, 149
 basal metabolic rate, 153
 clinical response to thiouracil ther
 apy, 153
 conclusions suggested by available
 data, 160
 dosage, 154

- duration of preoperative medication, 155
- effect of previous iodide therapy, 154
- effects on animals, 150
- effects on humans, 150
- perithyroiditis, 154
- propylthiouracil for thyrotoxicosis 161
- relapse, 153
- size of thyroid gland, 153
- theoretical possibility of carcinogenesis 158
- thiobarbital, 159
- thiouracil in acute thyrotoxicosis, 158
- thyroid tissue after thiouracil therapy 152
- toxic effects, 154 156
- illians* 153
- Thiourea, 150, 312 313
 - chemical structure, 150
 - compounds, 21
- Thomas O L* 83, 86, 91
- Thompson K H* 123 124, 146
- Thompson P K* 119, 148, 317 328 402, 404, 417
- Thompson H O* 110, 119, 148 301 304 317, 328, 402, 415-417
- Thurston E H* 91
- Thymicolymphatic constitution, 110
- Thyrocardias, 386
- Thyrocervical trunk, 71
- Thyrocricoid membrane 41
- Thyroglobulin, 92
- Thyroglobulin molecule, 20
- Thyroglossal cysts and fistulae, 40-42
 - aorta, 40
 - foramen cecum, 40-41
 - forms of ranula, 11
 - hyoid, 41
 - hyoid bone, 40 41
 - incisura of thyroid cartilage, 40
 - infrahyoid, 41
 - isthmus, 40
 - lingual raphe, 40-41
 - mediastinum, 40
 - multicocular, 41
 - persistent thyroglossal tract, 11
 - single, 41
 - sublingual, 11
 - subthyroid, 11
 - suprahyoid, 41
 - thyrocricoid membrane, 11
 - thyroid aplasia of cretins, 11
 - unilateral aplasia of adults, 41
- Thyroglossal duct, 41-42
 - ciliated columnar epithelium, 41
 - epithelium 229
 - median primordium, 11
 - squamous epithelium arising, 11
- Thyroglossal duct anomalies, 40
 - embryonic hyoid bone, 40
 - solid tumors, 40
 - thyroglossal cysts, 40
 - thyroglossal fistulae, 40
 - thyroid anlage, 40
- Thyroglossal rests, 372-373
 - aberrant thyroid tissue, 372
 - closure, 372
 - cyst, 372
 - misplaced epithelial cells of pharynx, 372
 - opening 372
 - removal of large pyramidal lobe, 373
 - sinus, 372
 - tumor, 372
- Thyroglossal tract, 26, 41-42
 - Bocdalek* 42
 - cyst, 42
 - external thyroglossal fistulae, 42
 - fistulous opening into the pharynx, 42
 - foramen cecum*, 42
 - Franz* 42
 - lateral ducts, 42
 - lingual duct, 42
 - persistence of the lumen, 42
 - retention cysts, 42
 - salivary gland acini 42
 - suppurating cyst, 42
 - suppuration, 42
 - thyroglossal cyst, 42
 - thyroid duct, 42
- Thyroglossal tumor, 50, 342

- Thyroid, 70-74
 glandules, 74
 Thyroid cancer, ix, 210
 Thyroid carcinoma with metastasis, 182-186
 adenoma malignum, 182 184
 administration of thiouracil, 185
 carcinoma in trachea, 186
 in cases of carcinoma with or without metastases but with hyperthyroidism, 182
 chemical analyses, 182
 colloid containing bony metastases, 183
 embryonal, fetal or simple adenoma, 183
 extensive pulmonary metastases, 185
 Frantz, 182 184
 frequency, 184
 Geiger counter, 183 184, 186
 Graves disease, 185
 Hamilton, 182, 186
 Hamilton, Soley and Eichorn, 182
 histology, 182
 Hürthle cell tumor, 183
 inability of carcinoma of thyroid to concentrate iodine, 182
 as indicator of functional activity of metastases, 185
 iodinization, 185
 ovarian struma, 184
 papillary forms, 183
 Pierson, 185 186
 radioactive iodine before operation, 182
 radiotherapy, 183
 storage of radioactive iodine in metastasis from thyroid carcinoma, 183
 thyroid carcinoma with metastases and hyperthyroidism, 184
 value of tracer doses of iodine, 183
 W'ard, 182
 Thyroid crisis, 300, 314, 358, 383, 390-395
 asphyxia, 393
 barbital compounds, soluble, 395
 Bayley, 391
 Buxton, 393 394
 circulating sympathomimetic toxin, 393
 Cohen and Gerard, 392
 emotional stresses, 393
 epinephrine, administration, 393
 fluids, 395
 frequently seen in poor risk patients, 134
 hemorrhage, 393
 infections, 393
 intravenous instillations, 395
 Kessler and Gellhorn, 392
 Maddock, Collier, and Pedersen, 392
 morphine, 395
 oversedation, 391
 oxygen deficiency, effect on myocardium and adrenal medulla, 393
 Perazzo, 392
 preoperative crisis, 391
 Raab, 393
 Ransom and Bayley, 391
 sedation, 395
 sodium iodide, 395
 sympathomimetic amines, 393
 symptoms, 392
 thiamin deficiency, 393
 thyroxin, 393
 trauma, physical and psychic, 393
 treatment, 395
 unusual exertion, 393
 warning signs and symptoms, 314
 Thyroid disease, 3
 Thyroid duct, 42
 Thyroid epithelial tumors, 59
 Thyroid extract, 19, 412
 Thyroid gland, vii
 hyperfunction, vii
 hypofunction, vii
 Thyroid gland in later life, 284-299
 Bruger and Rosenkrantz, 284
 change in later life, 286
 geriatrics, 284
 gerontology, 284
 Goldzieher, 284 285
 Hertzler, 284

- hyperthyroidism in aged, 291
- hypometabolism, 289
- hypothyroidism in elderly patient, 291
- senescence, 284
- treatment of thyrotoxicosis in the elderly, 294
- Vogeler* 284
- Thyroid hormone, 19 100
- Thyroid hormone and metabolism of inorganic salts, 100-101
 - Addisonian crisis 101
 - adrenal cortex insufficiency, 101
 - bone density, 100
 - chemical composition of bone 101
 - decalcification, 100
 - deposition of calcium, 101
 - deposition of phosphorus 101
 - hyperthyroidism, 100
 - secondary to pituitary dysfunction, 101
 - in hypothyroidism, 100
 - phosphorus metabolism, 101
 - retardation of bone formation, 101
 - urinary excretion of calcium 100
 - urinary excretion of sodium and chloride, 101
- Thyroid operations on children, 331
- Thyroid parenchyma, 30, 34
- Thyroid remnants remaining after removal of both lobes, 355
- Thyroid rests, 56
- Thyroid storm 311
- Thyroid tissue after thiouracil therapy 152
- Thyroid tissue lesions 26
- Thyroid underfunction, 15
- Thyroidea ima, 72 74
- Thyroidectomy, ix, 9-10, 17-18 21
 - in cats, 17
 - diet, 10
 - in dogs, 17
 - in the elderly, 295
 - instruments used in, 341
 - iodine, 10
 - mental rest, 10
 - in monkeys, 17
 - physical rest, 10
 - postoperative crises, 9
 - in rats, 17
 - wounds, drainage, 354
- Thyroiditis, 11, 13, 241-273
 - acute, 11, 13
 - acute nonsuppurative thyroiditis, 242, 245 247
 - acute suppurative thyroiditis, 242-245
 - calcification, 241
 - chronic, 11, 242
 - Cole Womack, and Gray*, 241
 - constitutional upset, 242
 - Farrant*, 241
 - fibrosis, 241
 - from adrenal dysfunction, 254
 - from overstimulation by thyrotropic hormone of pituitary, 254
 - grave toxemia, 242
 - Hashimoto's disease, 242, 263
 - hemorrhage into the stroma, 242
 - hyperfunction, 241
 - infection, 243
 - inflammatory reaction to physiologic and pathologic states of stress, 241
 - maintenance of homeostasis, 241
 - Parmley and Hellwig*, 242
 - Riedel's struma, 11, 242
 - Roger and Garnier* 241
 - stroma, 241
 - struma lymphomatosa or lymphomatoid goiter, 242
 - strumitis, 242
 - subacute, 11, 13
 - suppuration, 242
 - surgery, 13
 - trauma, 243
 - vascular damage, 241
- Thyronine, 106
- Thyrotoxicosis, 20
- Thyrotoxic symptoms, 5
- Thyroxin, 18, 21
- Thyrotropic extract, 101
- Thyroxin, 22, 94, 126, 393
 - content of plasma and peripheral tissue, 126
 - polypeptide, 94
 - secretion, 22

- Time of origin of function of thyroid
 60
 first differentiation of the follicles
 within the lumina 60
 follicular differentiation, 60
 functional fetal tissue, 60
Gorbman and Evans, 60
 hormone as morphogenetic factors,
 60
 hyperthyroidism in pregnancy, 60
 radioactive iodine, 60
 radioautograph technique, 60
- Tonus in voluntary muscles, 280
- Torneux F*, 64
- Total hemithyroidectomy 367
- Total thyroidectomy, 367
 results 102
- Tourish, W. J.*, 165
- Toxemias, 282
- Toxic adenoma, 105 206
- Toxic diffuse goiter 5, 7 11, 214, 340
 acini 7
 basal metabolic rate, 9
 follicles, 7
 hyperplasia, 7
 iodine, 9
 Lugol's solution, 9
 lymphoid tissue, 7
 papillary projections 7
 proliferation, 7
 subtotal thyroidectomy, 8
 surgery, 9
 tachycardia, 9
- Toxic diffuse hyperplastic goiter, 172
- Toxic effects, 156-158
agranulocytosis, 156-157
 anemia, 157
Bishop and Rauson, 157
 conjunctivitis 157
 drug fever, 157
 edema of feet, 157
 granulocytopenia, 156 157
 jaundice, 157
 leukopenia, 157
 liver damage, 157
 lymph node enlargement, 157
Moore F D, 156 157
 myxedema, 158
 per cent 156
 purpura 157
 psychotic manifestations 157ⁿ
 skin reactions 157
 swelling of lacrimal and salivary
 glands, 157
 urticaria 157
Van Winkle 156 157
- Toxic goiter, 20, 110 204 207
- Toxic nodular goiter 5 9, 214
 basal metabolic rate 6
 cardioaccelerator centers, 6
 cervical sympathetic ganglia 6
 colloid degeneration 7
 dilatation of the bronchial tubes 6
 exophthalmos, 6
 formation of cartilage 7
 hemorrhage, 7
 hyperplasia, 7
 hypersecretion, 9
 increased aeration in the lungs 6
 Mullerian muscles 6
 ocular symptoms, 6
 orbitalis 6
 scar tissue, 7
 surgical enucleation, 7
 sympathetic fibers, 6
 sympathetic nerve fibers 6
 sympathomimetic toxin, 6
 tachycardia, 6
 thyrotoxic symptoms, 6
 tremor, 6
 voluntary muscles, 6
- Toxic symptoms 5
- Toxicity, 8
- Trabeculae of epithelium, 208
- Tracheal artery, 72
- Tracheal cartilages, 72
- Tracheal obstruction 249
- Tracheal plexus, 71
- Tracheocele, 15
- Tracheoesophageal groove, 75
- Tracing the effects of goitrogenic sub
 stances, 170
- Tracing effects of sulfonamides 169
- Transcellular release of colloid 83
- Trapl*, 56
- Trauma, physical and psychic, 93

- Water metabolism 100
 administration of thyroid, 100
 Brothby 100
 Byron 100
 loss of sodium salts, 100
 normal water metabolism, 100
 plasma volume, 100
 potassium salts 100
 Thompson 100
 Wason H L 218 219 232, 240
 Wazala M 34 64
 Webster B 149 161
 Weeks C 76 91
 Wegelin C 67 91, 217 240
 Welch, C F 334 337, 339
 Weller G L 34 33 64 138
 Wells H G 38 65
 Wellis H 217 218, 232 240
 Werner S C 165
 Weston W 119
 Warton T 15 17 25
 White House Conference on Child
 Health and Protective Nutrition
 120
 Wilder, R M 307, 328
 Wilkins L 100 119
 Williams A 118
 Williams R G 81 91 92 119
 Williams R H 150 153 160 161
 164 306, 312 328, 410 417
 Williamson, G S 65, 264 265 273
 Willis, F A, 321 328
 Wilson, H G 195
 Wilson L B 217, 240
 Winterarter, H, 65
 Winkler, A W, 128 132, 134 135,
 147, 312, 327
 Winter E A, 138, 147, 381
 Wohl M G, 20, 25, 52, 54, 65, 130
 Wolfe J M 90, 288, 289
 Wölfler 59
 Womack N A 241, 243, 247-248,
 254, 264 268, 270, 272 273, 382,
 399
 Wood, W B, Jr 311, 327
 Woodman D 388 391
 Woolard H H 65
 Wright A W 247, 264, 271 272
- X
- X factor, 134
 X ray treatment 317
 X secretion 122
- Y
- Young E L Jr 65
 Young T O 117
 Yuzurba 139
- Z
- Zelle O L 254 262, 272
 Zesas D G 17 25
 Ziegelman E F 75 76 91
 Zordek, H 20, 25, 95, 120

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and

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